

SPOLIA ANATOMICA ADDENDA I

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TWENTY-SEVEN FIGURES

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PERFORATE SPHENOIDAL SINUSES WITH SUBDURAL DIVERTICULA

Specimen *a* is from the body of a white man, twenty-eight years of age, who died of tuberculosis.

There are two sphenoidal sinuses, as usual, in this specimen; the right sinus extends several millimeters across the median line. The septum is located in almost a sagittal plane lying 2 to 3 mm. to the left. The form of the right sinus is oval with its long axis—which is practically parallel to the upper surface of the basilar process of the occipital bone—making an angle of

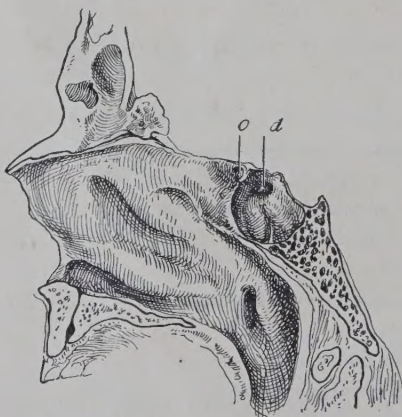


Fig. 1 Developmental defect in the lateral wall of the sphenoid and sphenoidal diverticulum; side view.

approximately forty-five degrees with the vertical. This diameter measures 25.5 mm., the vertical one 15 mm. and the transverse (right to left) 18 mm. The lining membranes of the sinuses are thin and they are not abnormally adherent anywhere. The roof of the right sinus is very thin, measuring only 0.35 mm. (by micrometer caliper) directly beneath the sella and a little to the left of the median line; its minimum thickness is only 0.5 mm.

Although the configuration of the left sinus is similar to that of the right it is much smaller, measuring only 11 mm. in a transverse (right to left) diameter and 22 mm. in the longest

oblique direction; it too is normal in appearance. The combined sinuses extended only about half way beneath the sella. The ostia are normal in size and position.

The nasal cavity is capacious but normal in appearance, and the conchae, except the superior, are small. There are four conchae on the left side, the posterior ethmoidal cell opening into the supreme meatus.

At about the midpoint of the ventral (anterior) portion of the lateral wall of the right sinus immediately beneath its roof there is an oval defect (fig. 1*d*) The longest diameter of this oval defect measures 7 mm. and extends antero-laterally, lying almost in a horizontal plane and making forty-five degrees with

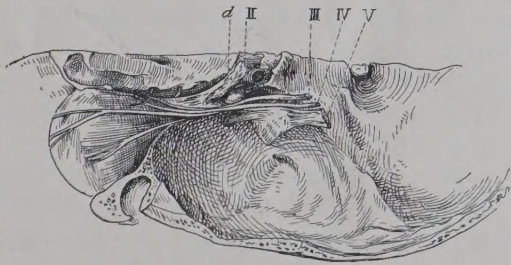


Fig. 2 The same as figure 1; cranial view.

a sagittal plane. The short diameter measures only 4.5 mm. Through this opening a diverticulum of the sinal lining, which is 6 mm. long, protrudes into the subdural space. The wall of this diverticulum is very thin, nowhere adherent to the exceedingly thin (0.5 mm.) but regular margin of the defect and can be inverted with entire ease. It extends slightly forward and upward into a triangular space bounded by the optic nerve antero-medially, the carotid artery postero-medially and the reflection of the dura laterally (fig. 2) The dura, which surrounds the base of the diverticulum on all sides, does not envelop or cover the defect but merely comes into contact with the encephalic surface of the bony margin bounding the defect. Hence it is evident that the mucous diverticulum extended directly into

the subdural space and must have been in direct contact with the arachnoid.

There is no corresponding or other defect in the wall of the left sinus but the corresponding region is marked by a depression which lies in the base of the posterior root of the lesser wing. This root is absent on the right side. The anterior clinoid process on the left side joins with the middle, forming a complete foramen for the carotid artery. That on the right side unfortunately had been partly removed but the condition of the middle clinoid process, which is wholly intact, shows clearly that it was not joined to the anterior on this side, and the lateral wall with its dural reflection shows that the posterior root of the clinoid process was absent on this side.

The anterior and middle ethmoid cells and the frontal sinus were large but the posterior ethmoid cells were extremely small, being 3 to 4 mm. in size.

Specimen *b* is from the cadaver of a man thirty years old, who also died of tuberculosis.

The left sphenoidal sinus in this specimen is somewhat larger than the right and extends completely beneath the hypophyseal fossa, being separated from the pons by an exceedingly thin bony wall only 0.37 mm. thick. The hypophyseal fossa is large and long, in a dorso-ventral direction. The dorsum sella is T-shaped in section, low (5 mm. high) and composed of a thin plate of bone which bears the large (by comparison) posterior clinoid processes. The floor of the sella formed the dorsal (posterior) half of the roof of the sinuses.

The ventral (anterior) half of the lateral wall of the left sinus contains a defect similar in position and character to that in the preceding specimen. This defect is oval also but somewhat larger than the preceding for it measures 6.5×4.5 mm. The bony margin bounding it protudes slightly intra-cranially, forming a small cuff around the defect; this margin is only 0.25 mm. thick.

The diverticulum of mucous membrane which protrudes through this defect extends fully 3.5 mm. beyond the plane, extending across the dural reflections over the optic and oculo-

motor nerves; it is slightly enlarged distally. Although the lining membrane of the sinus is somewhat thicker than that of the preceding case, it is nowhere adherent and could be easily inverted. The relations of the diverticulum to the surrounding structures are exactly the same as in the previous specimen. It has a total length of 6 mm. and a width of 7 mm., in a line parallel to the optic nerve, and a width of 4.5 mm., in a cranio-caudal direction. Since a thin bony rim extends intracranially around the defect, for several millimeters the optic nerve lies more above than medial to the defect. This bony rim also covers the ventral knee of the carotid artery.

The dorso-ventral diameter of the left sinus is 29 mm. and it extends several millimeters beyond the median line, which it intersects somewhat obliquely, the ventral half of the septum lying a trifle to the left of the median line. This sinus does not extend beneath the hypophyseal fossa on the right side except at its most caudal portion, although laterally to the right it extends beneath the middle cerebral fossa.

Just as on the left side of the previous case, there is a depression in the lateral wall of the right sinus in a position corresponding to the defect on the left side. As before, this depression was covered by the posterior root and in part also by a bony extension from the anterior to the middle and to the posterior clinoid process, representing the ossified ligamenta interclinoidea not infrequently present. On the left side, on the contrary, there is no such extension from the anterior to the middle, but only from the middle to the posterior, clinoid process.

The finding of these defects in two subjects, the skull of neither of which was damaged by disease or injury, among only eight cadavers simultaneously under dissection, remotely suggests John Burroughs' dictum that "the number of birds one sees depends on the number one looks for," for I cannot believe that these instances are isolated cases, especially not after I have examined a small series of skulls with especial reference to the shape, form and position of the posterior root of the lesser wing and the osteology of the surrounding region. It is, for example, comparatively common to find a depression—i.e., an evagination

of the sphenoidal sinuses into the base of the posterior root—and in one cleaned remnant of a skull found in the laboratory one of the sphenoidal sinuses communicated with the cranial cavity at exactly the same place as in the preceding specimens. Although the lesser wing of the sphenoid had been removed in this specimen it was evident from the character of the margin of the defect in the lateral wall, and from the character of the wall itself, that it is not improbable that the defect was present in this specimen also before it was cleaned for only a very slender posterior root could have been present. However, the mere presence of a very slender posterior root, or perhaps even its absence, is not necessarily an indication that the sphenoidal sinus is not completely separated by bone from the cranial cavity. The absence of this root is probably of significance only if the sphenoidal sinus is as large or larger than normal, or perhaps still more accurately, only when there is a tendency to extend the sinus laterally in the region of the base of the root. Just why absorption should be especially active here at the junction of the pre- and basi-sphenoids, I do not know, and it is possible, of course, that tension exerted through the root in consequence of unequal growth after its fusion with the lateral wall may cause evagination of the sinus into the base of the root and its absorption.

The absence of the posterior root in both the above specimens must have left a weak point in the wall at this region. Since the reflections of the dura over the carotid artery, the second nerve, and over the third, fourth and sixth nerves in the adult lie at a higher intracranial level than the wall of the sinus, it is evident that the dura at one time must have been depressed over this region in order to clothe the portion of the lateral wall later occupied by the defect. In pre- and early post-natal life, to be sure, there could have been no such dural depression, but with the change in contour and in the relation of the different portions of the sphenoid bone and the extension of the air sinuses, with approaching maturity of the bone such a condition was bound to appear. Since in these cases the lateral wall of the sphenoid was not reinforced by the posterior root, as is normally

the case, it might be assumed that this region formed a point of least resistance to the developing and encroaching air sinus, were it not for the fact that other portions of the sinal wall are not reinforced and yet no perforations or defects result. That the increased intra-sphenoidal air pressure associated with such occasional phenomena as sneezing, coughing or forcible and obstructed expirations of any character, could be responsible for local atrophy of the bony wall and the underlying dura seems decidedly unlikely, although the form of the diverticula and the bony margin of the defects seems to suggest this. Indeed, no other explanation seems to fit the anatomical findings. But until we know more about the cause of the development of the air sinuses and the factors which control their development in the different directions, it seems quite futile to speculate on the genesis of these peculiar defects.

It seemed highly probable to me, at first sight, that the dura must have covered these diverticula, but that it did not do so except at the very beginning of their extension through the bone is beyond question. Indeed, the perforation of the dura by the diverticula is the most interesting and unexpected thing. Moreover, it would have seemed likely that the cerebrospinal fluid, the other meninges and the brain substance might have forced these diverticula of mucous membrane back into the sinuses, or rather prevented their protrusion. It would also seem as if one might have expected a diverticulum of the arachnoid, accompanied or unaccompanied by brain, to extend into the sinus as a result of the unopposed intracranial pressure. Moreover, since a defect was produced in the dura, it also seems as though the arachnoid should also have yielded to the same influences. Unfortunately, the brains had been removed from both these skulls, but the durae were undisturbed in these regions. The presence of the protruding diverticula is conclusive evidence, however, of the fact that practically no intracranial pressure was exerted upon them, for their extremities were entirely unattached to the durae and their inversion into the sinuses was prevented only by atmospheric pressure. Besides, had they been at all firmly attached to the arachnoid it is more than

likely that a tag of arachnoid would have remained attached to their distal extremities when the brains were removed.

The only investigators who mention any defects whatsoever in the lateral wall of the sphenoid are Zuckerkandl ('82), Spee ('96) and Onodi ('03). The first spoke of having noticed dehiscences and small defects in the lateral walls, and the latter of small defects in the region of the sulci carotici in a juvenile skull. Onodi, who examined 4000 entire and several hundred cut skulls, found vascular sulci and foramina in the lateral wall and also larger or elongated dehiscences in these vascular sulci. But neither he nor Gibson, who recently examined 85 specimens, found any defects comparable to those here reported. Onodi also emphasized the fact that such dehiscences as he found may result from traumata, pathological conditions and senile atrophy, as well as be artifacts or developmental anomalies.

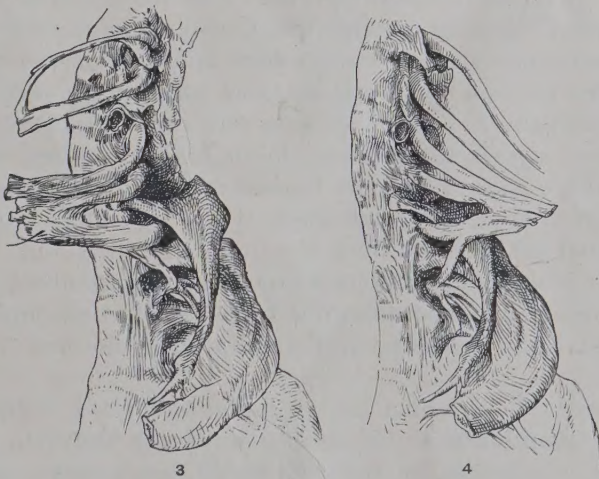
Since small defects in the lateral walls in the region of the carotid sulci—and in other places, for that matter—are seen not very infrequently in cleaned and dried skulls, it is evident that such skulls do not furnish proper evidence regarding the actual frequency of these abnormalities. If the walls of the sinuses are exceedingly thin they are easily injured when the dura is stripped and still more easily eroded in the cleaning. Hence, skulls in which the durae have not been removed can alone be regarded as furnishing reliable evidence.

Since the clinical significance of such defects in the lateral osseous wall, accompanied or unaccompanied by protrusions of the lining mucosa into the subdural space, must be evident to everyone emphasis on this matter is unnecessary.

CERVICAL RIB ASSOCIATED WITH EIGHT CERVICAL VERTEBRAE

The body from which this specimen was obtained was that of a female Swede 38 years old. There was nothing especially peculiar about the cervical rib which was present on the left side (fig. 3) except that it was well formed. It reached to within 2 cm. of the sternum and measured 7 cm. in length, along its concave border from head to tip, and the same dis-

tance along its convex dorsal border from the prominent articular tuberosity of the eighth cervical vertebra. The distal extremity of the rib was thickened and articulated with the upper surface of the first thoracic rib, about 2 cm. from the costo-chondral junction of the latter. A true articular capsule and an articular surface were present. The one on the first thoracic rib was about 3.5 mm. across. Both articular surfaces were covered by cartilage, and from the lateral surface or the distal extremity of the cervical rib a narrow but strong ligament, almost tendin-



Figs. 3-4 Cervical rib and brachial plexus.

ous in character, extended to the sternum. It ran parallel and directly cranial to the border of the first thoracic rib. Only slight mobility was possible between these two ribs, which mobility was greatly increased by section of the articular capsule at the distal extremity of the rib.

The head of the rib is small, the neck broad and flat, the tubercle comparatively large, and the shaft looks decidedly twisted because of the presence of a prominent groove formed

by the medial fasciculus of the brachial plexus as it crosses the shaft obliquely. The distal extremity of this rib is somewhat thickened.

The lower surface of the broad thin neck and the upper surface of the distal third of the shaft are grooved by the *ninth* cervical nerve; and the medial fasciculus of the brachial plexus and the cranial surface of the neck and the medial half of the body by the eighth nerve. The very thin and sharp medial margin of the broad neck lies between these two constituents of the brachial plexus, which join directly distal to this sharp border, 3 cm. distal from the head. This sharp medial margin also bears a slight impression from the subclavian artery. The communication from the first thoracic intercostal nerve did not cross this rib but ran along its lower border (the plexus was drawn cranially in figure 4) joining with the ninth nerve before the latter crossed the cervical rib to reach its upper surface, upon which it lay nearly to its extremity. If the subclavian vein also made a slight impression it was in common with the artery and not separate from it.

There is no separate extra rib on the right side, but a thin broad fibrous band extends from the prominent transverse process of the eighth vertebra to the mid-point of the first thoracic rib.

The cervical vertebrae are all normally formed; there is no sudden transition from the spinous process of the sixth to the seventh, or from the latter to the eighth, but merely a gradual increase in length of the spinous processes from the second to the eighth, and from the latter to the first thoracic. The extra vertebra had the character of a thoracic vertebra on both sides, although the two halves were not symmetrical. This also agrees with the statement of Bardeen ('00) who found in an examination of 59 spines that "There was some variation in the form of the vertebrae on the two sides of the body but in none of the bodies which we examined for the purposes of the present study was a given vertebra of different type on the left side of the body from what it was on the right side." The asymmetry was due to the presence of the rib, and hence of an articular facet on the

body and the transverse process on the left side, and the presence of a long transverse process with a foramen on the right. The dense band of fascia mentioned above arose from the extremity of this transverse process and extended to the upper border of the first right rib. The unusual length of the transverse process, as well as the contained foramen, confirm Todd's conclusion that all elongated transverse processes in this region are



Fig. 5 Cervical and thoracic curvatures in a spine with eight cervical vertebrae.

to be regarded as resulting from the attempted formation of rudimentary ribs.

The vertebral artery entered the transverse foramen of the fifth vertebrae on the right and that of the sixth on the left side.

As is usual, the cervical curvature as represented in figure 5 was markedly accentuated. As judged by the alignment of the

spines from the dorsum, there is no more than the usual amount of scoliosis, but there is a rather decided curvature to the right in the regions of the bodies of the 4th to 8th dorsal vertebrae. The maximum curvature is located opposite the body of the sixth cervical vertebra and the whole curvature is accentuated by the presence of flattening of the bodies of the 4th to 8th vertebrae on the left side. Since there is no such flattening on the right side, the convexity of the scoliotic curve is less evident than its concavity. The flattening of the bodies is so extensive that it can scarcely be attributed to the aorta alone. The bodies and the discs of the cervical vertebrae are only very slightly reduced in thickness and the cervical spine is hence longer than usual, especially if compared with individuals of corresponding stature. The increase in cervical curvature seemed to be compensated for, at least partly, by an accentuation of the dorsal curvature but no reduction in length compensatory to the cervical increase was evident; nor was there any reduction in the number of vertebrae in other regions. Twelve dorsal, five lumbar, five sacral and three coccygeal vertebrae were present.

The brachial plexus was normal in formation and distribution. It was not shifted cranially but caudally with the extra vertebra. This was the case of the cervical plexus also. Hence it is evident that in this case the presence of the plexus did not have any inhibitory effect upon the formation of an extra rib, as Patterson suggested. Nor was there any pre-fixing of the plexus, as emphasized especially by Jones ('13). The contribution from the first thoracic nerve was fully as large as normal, and this case then stands in striking contradiction of Jones' statement that

Just as varying grades of imperfection of development of the first thoracic rib are the outcomes of varying degrees of postfixation of the plexus, so the varying grades of perfection in the development of a cervical rib are the outcomes of varying degrees of prefixation of the plexus. And just as the postfixation may readjust itself with the rib elements at a lower level, so may the prefixation readjust itself at a higher level.

This generalization would also seem to be contradicted by the case reported by Frank ('14).

The very intimate relation of the ninth and first thoracic nerves to the cervical rib would seem to imply that considerable nervous disturbances probably resulted from pressure upon them, as emphasized by Goodhart ('09), Todd ('12), Thorburn ('05) and others.

Since such an excellent discussion and a summary of the literature on cervical ribs is given by Le Double ('12) and also by Streissler ('13) I shall only add that my own experience confirms Le Double's statement that variations in number of the cervical vertebrae are exceedingly rare. Nor does Streissler mention a case of supernumerary cervical vertebra accompanied by a cervical rib, although his summary covers 80 pages and includes 297 citations from the literature.

THE EFFECT OF UNILATERAL ABSENCE OF A VERTEBRA ON THE PRODUCTION OF SCOLIOSIS

A priori, one would be likely to conclude that the failure of development of the right or left half of a vertebra would result in a very evident, even if not in a marked, deformity of the spine. That this is not an inevitable result, however, was shown in the body of an adult male from which the specimen represented in figure 6 was taken. In this case only a slight deviation in the alignment of the spinous processes was noticeable after skin, fascia and some of the dorsal musculature had been removed, so that the true nature of the anomaly was not noticed until the thorax had been opened and the relations and the marked ventral scoliosis were revealed.

There were also a number of other abnormalities in this cadaver. The twelfth ribs were exceedingly small, as shown in figure 7, and the tenth and eleventh were long floating ribs. The xiphoid was long, curved, narrow, and completely ossified. The twelfth ribs, which measured 2 mm. in length, are symmetrical. Each is provided with a small articular facet 3 mm. in diameter on the body of the vertebra, and with a true articular capsule; they were slightly movable. Since the head and neck of the cadaver had been removed before the body was received

at the laboratory it is impossible to speak with certainty regarding the number of cervical vertebrae but even assuming that the normal number was present—according to Le Double six cervical vertebrae occurred in only 0.14 per cent of 1420 fetal, infantile

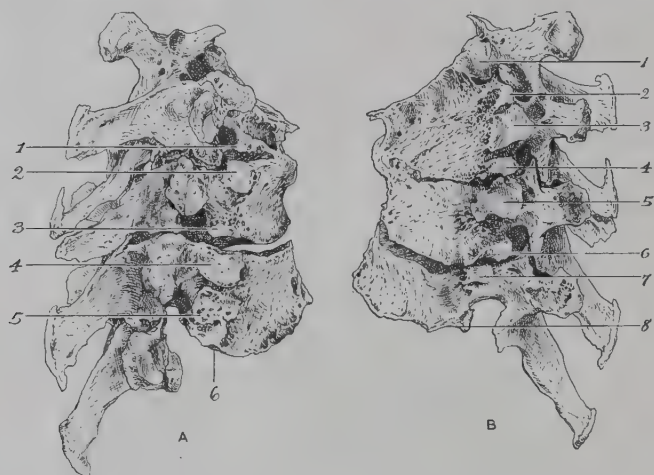


Fig. 6 Unilateral absence of half a vertebra and oblique fusion of the fourth to eighth thoracic vertebrae.

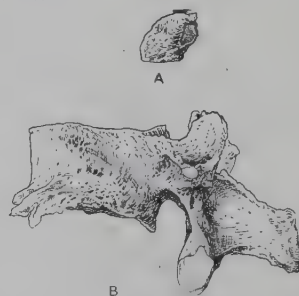


Fig. 7 Twelfth thoracic vertebra and rudimentary rib.

and adult vertebral columns reported in the literature—the total number of pre-sacral vertebrae is only twenty-two.

There are twelve vertebrae in the thoracic but only three in the lumbar region, the fourth lumbar being completely incor-

porated in the sacrum, which is composed of six vertebrae. The spinous process and the lamina of the first sacral are entirely distinct and the inferior intervertebral articular facets are preserved completely on the right, and almost completely on the left, side of the first sacral vertebra. But the sacrum differs in no essential respects from many similar sacra seen in every laboratory. As figure 7 shows, the thoracic vertebra—the twelfth—which bears the very small twelfth ribs has the characteristics of a lumbar rather than of a thoracic vertebra. This applies especially to the character of its spinous process and the direction of the surfaces of the superior articular facets. The transverse processes of the tenth and eleventh dorsal vertebrae bear no articular facets and have the characteristics of the normal eleventh and twelfth dorsal vertebrae. The corresponding ribs also have the characteristics of the normal eleventh and twelfth ribs. Hence if this, the twelfth dorsal numerically, be regarded as a lumbar vertebra in spite of the presence of rudimentary ribs, and the fifth lumbar be regarded as having fused with the sacrum, as is evidently the case, the normal number of five lumbar vertebrae is accounted for. This, however, leaves only eleven dorsal vertebrae represented by only eight distinct bony elements. The first three and the last four of these eleven dorsal vertebrae are separate bony elements quite normal in form and size. The eighth independent element is a bony complex represented in figure 6, and—as indicated by the number of ribs and transverse processes—should be composed of four vertebrae. There are five independent spinous processes, however, as shown in figure 6. On closer inspection, however, it will be seen that the second and third spinous processes are really only half processes of two different vertebrae each of which is represented by half a vertebra located on opposite sides of the body. The second spine belongs to a half vertebra on the left and the third spine of the complex belongs with a half right vertebra which is fused with the body of the succeeding vertebra. This relationship becomes clearer upon examination of the bodies. As seen in figure 6, *a* and *b*, showing right and left sideviews respectively, there are only three bodies in this complex. Moreover, the right portion

of the body of the first vertebra in the complex is reduced decidedly in thickness and the left portion is decidedly enlarged. The former bears only a small articular demi-facet and the latter a large and small demi-facet, and one large entire articular facet on its body. Hence it would seem that this portion of the complex represents a little less than one vertebra on the right and two vertebrae on the left side. The same thing is indicated by the presence of two transverse processes on the left and one on the right side and by the presence of a dorsal ridge, which clearly marks the line of fusion of the two lamina on the left side, and by a sulcus between the large middle articular facet on the left side of the body, which divides this large facet into two parts one of which resembles a demi-facet. The other no doubt represents a demi-facet also, although it looks like a whole facet and is large enough for one. Since a single rib—the fifth articulated here—this composite articular surface evidently represents only two demi-facets of adjoining vertebrae.

As viewed from the front, the upper surface of the body of the first vertebra in the complex slopes decidedly from left to right and although this great inequality in the thickness of the body was compensated for largely by difference in the thickness of the intervertebral disc and very slightly also by a slight inequality in the body of the third dorsal vertebra, it nevertheless caused a short but marked scoliosis, noticeable only ventrally.

A reference to figure 6, *a*, will also show that there was a shifting caudally of the lamina, transverse processes and pedicles on the right side, as a consequence of which the last lamina and transverse process, although normal in size and shape, are left without a pedicle. All the transverse processes, lamina and pedicles on the right have been shifted one vertebra caudally, and actually belong to the bodies one vertebra farther cranially. This asymmetrical bilateral error in segmentation also explains the presence of the two half spinous processes and is further confirmed by the presence of two half and one whole articular facets on the right side of the body of the last vertebra of the complex, as shown in figure 6. Hence it is evident that the right

half of the last composite vertebra, in this complex of four, articulated with three ribs, as did the left side of the body of the first. Since the lamina and intervertebral articular facets of the first two vertebrae are fused on the left side of the complex, only two normal articulations remain on this side, although three are preserved on the right. One of the articular facets on the left side is also on a pedicle.

The particular interest attaching to this error in segmentation lies, I take it, in the fact that the absence of one half segment was accompanied by the oblique fusion of dissimilar halves of succeeding segments, with consequent production of a floating lamina and transverse process, both of which have a normal form and size.

Aside from a few minor abnormalities present in this cadaver, the most interesting thing was the position and blood supply of the kidneys. The lower pole of the left kidney reached only to the level of the tenth ribs. This kidney was small (9.3×4.7 cm.) and received its main blood supply from a renal artery which arose at the level of the origin of the superior mesenteric. This artery bifurcated several centimeters from the medial border of the kidney, which it penetrated directly cranial to the pelvis. An additional large artery, which entered the medial surface about midway between the hilum and the lower pole, arose in common with the inferior mesenteric and a right renal 5 cm. cranial to the bifurcation of the aorta. Directly from the apex of the lower pole an accessory vein emerged and emptied into the vena cava.

The right kidney, which was considerably larger, measured $11.7 +$ by $5 +$ cm. Its lower pole reached the level of the lower border of the lumbar vertebrae, almost half of the renal mass lying caudal to the bifurcation of the aorta. The superior pole reached the middle of the second lumbar vertebra. This kidney had three renal arteries. The main renal took its origin from a trunk common to the inferior mesenteric and accessory left renal, and bifurcated about 2 cm. from the renal mass. A second renal artery arose from the lateral border of the right common iliac about 1 cm. below the bifurcation of the aorta. From here it took a slightly upward course, passed dorsal to the

kidney and bifurcated about 2 cm. before reaching the lateral renal border. One branch ended on the lateral border and the other on the ventral surface.

A third renal artery arose from a trunk common to the middle sacral and fifth lumbar arteries. This vessel emerged between the two common iliac arteries, then curved abruptly to the right, crossed the right common iliac ventrally and bifurcated at the border of the vena cava, the branches entering the ventral surface of the kidney 1 cm. lateral to the medial border.

Two large renal veins emptied directly into the vena cava. The largest, which was located farthest cranially, arose near the lateral border of the ventral surface between the lower and middle thirds by two trunks, which soon joined and emptied into the vena cava about 2 cm. cranial to the superior pole. The second vein arose by two branches, coming from the dorsal and ventral surfaces respectively, near the medial border of the superior pole.

The ureter arose mainly from a larger pelvis lying on the ventral surface between the upper and middle thirds and from three small accessory pelves located on the ventral surface of the middle and lower thirds. Each of these pelves had a ureter which joined the main ureter separately.

FUSION OF THREE CERVICAL VERTEBRAE

The specimen found in a skeleton of *Troglodytes savagei* is composed of the 3rd to 6th cervical vertebra, inclusive. As the illustration (fig. 8) shows, almost complete fusion has occurred. The three transverse processes on the left side, although very different in form, are quite separate, however. The articular processes are fused completely but the location of the individual processes can still be determined because of the presence of sulci in the inter-articular regions.

The extremities of the right transverse processes of the third and fourth vertebra are fused in such a way as to form an almost complete bony ring, through which the fifth nerve passed ventrally. The distal portion of the transverse process of the third

is absent on this side but the base containing the transverse foramen is preserved. The bodies of these vertebrae are fused so completely that the exact limits of the individual corpora can nowhere be detected.

The character of this splendidly preserved specimen shows clearly that the fusion did not result from injury or disease but is a simple case of embryonic fusion. The remaining cervical vertebrae are normal in size and number, there being 13 dorsal, 3 lumbar, 2 sacral and 3 coccygeal vertebrae. A marked dorsal inclination or retro-flexion of the dens epistropheus is present



Fig. 8 Fused third to sixth cervical vertebrae of a gorilla.

and may be due to the lessened mobility of the cervical spine resulting from the fusion of the 3rd to 6th vertebrae.

AN UNUSUAL THORACIC DUCT

The careful statistical study made by Davis '15 has supplied us with a better basis for grouping anomalous ducts and for judging the frequency of the different types. Since a case of double duct, observed by me some years since, differs from those recorded by Davis, Svitzer, von Patruban, Wutzer and others, it seems worth while to give a short description of it from the sketch and notes at hand.

A cysterna chyli formed by the confluence of three lymph vessels was present in the usual location. From it a large left thoracic duct extended cranially and emptied into the subclavian vein after being joined by the left cervical trunk. But in addition to the left thoracic duct a smaller duct ran to the right from the cysterna chyli and then extended cranially parallel to the left duct, continued directly with the left cervical and joined the left thoracic duct by a transverse branch in the bronchial region after receiving a large bronchial trunk. In addition to being double, this specimen of the thoracic duct was interesting in the fact that the right cervical trunk joined the right thoracic in the thorax in the retro-bronchial region and sent a transverse communicating branch, which joined the left thoracic duct after receiving a large bronchial trunk.

A LARGE PHRENICO-HEPATIC ARTERY

Although the occurrence of small hepatic branches from the phrenic arteries is mentioned in all anatomies as normal I have been unable to find a description of a large vessel such as noted here. The vessel in question, which was fully 2.5 mm. in caliber, arose from the right phrenic and entered the fossa ductus venosi near its cranial extremity. It then divided, sending one branch cranially into the left lobe the other branch running caudally along the fossa. A few centimeters from the point of bifurcation a second branch was given off to the left lobe at about the midpoint of the vessel but the main trunk extended onward to the porta hepatis, where it divided into three branches which entered the quadrate lobe. The phrenic itself arose directly from the aorta opposite the left renal artery and gave off a supra renal branch before reaching the diaphragm.

CORPORA LIBERA ABDOMINALIS VERA ET POTENTIALIA

In a former article I have reported the finding of true appendices epiploicae (not coli) and discussed their genesis and significance. Since then I have found two more cases of appendices and one case of corpus liberum.

One of these appendices was found in the ventral surface of the great omentum of a cat; it is shown in figure 9. Its actual length *a-b* was 8.5 mm. and the cylindrical vascular tip, which very closely simulated a hemal node, was 2 mm. long and 1.3 mm. in caliber. The vessels going to it were not visible in the gross.

In figure 10 a much larger fatty bovine omental appendage is represented. Its greatest width was 14.5 mm. and its length 22.2 mm. The capsule is thin and the whole appendage has the appearance of normal fat.

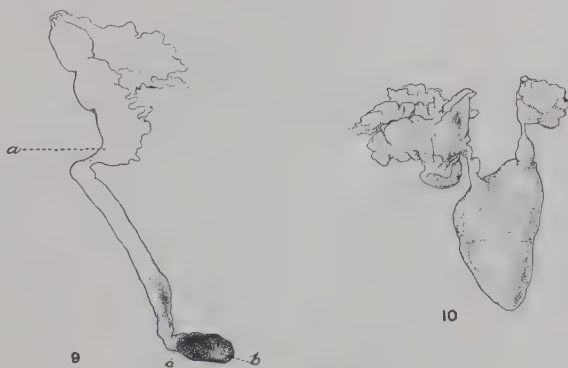


Fig. 9 Omental appendage from the cat; actual length, *a-b*, is 8.5 mm.; length of hemal nodule at tip is 2 mm. and its diameter is 1.3 mm.

Fig. 10 Omental appendage from a steer; actual size 14.5×22.2 mm.

The third specimen was found in a small cavity on the internal surface of the ventral wall of the greater omentum of the body of an adult male. It is oval in form and measured 2×1 cm. It is smooth and soft and was contained within a small sac about twice its size, which was located on the internal surface of the ventral reflection of the great omentum. It could easily be rolled between the fingers and the character of its surface, as well as its form, suggest that it had often been rolled about by the action of the peristaltic movements on the great omentum.

On section this body is found to have a well-defined connective tissue capsule, 0.5 mm. thick, which contains a partially degenerated fatty material. Although no histological examination

was made there is little likelihood that this body was other than a fatty omental appendage, such as that shown in figure 10. The fact that it was contained in a small omental bursa is likely accounted for by a slight inflammatory reaction which probably accompanied its detachment from the omentum. The mere process of torsion of the pedicle which precedes and accompanies separation would alone favor the exudation of a sufficient amount of serum to cause omental adhesions about the appendage. However, since these adhesions would be unlikely to form over the whole surface of the appendage, the continuous effects of peristalsis could later free it and convert it into a corpus liberum within its own small sac, instead of within the omental bursa.

Upon the genesis of a thickened connective tissue capsule from a very thin peritoneal layer I have no information to offer. That matter has been discussed often since Virchow called attention to the thick cartilaginous capsules which frequently surround loose bodies. However, since seeing the report of the extraordinary large free body found in the abdominal cavity by Campbell and Owen ('14) I am prompted to add that no evidence whatever for the idea that free bodies continue to grow in size after detachment was found in any of the cases which came under my observation. Nor can I say I should have expected to find any, for the evidences of degeneration present even in very small loose bodies, as well as the evidences obtained from tissue culture and from corpora libera articulationes—corpora oryzoidea, joint mice—speak very strongly against such a supposition. Moreover, it is well known that the presence of comparatively small loose bodies often necessitates operative interference and the larger the uncalcified body the greater the danger from degeneration if detachment has been sudden.

BIZARRE LYMPH FOLLICLES

During my investigations on hemal nodes, especially of the sheep, I was frequently impressed with the singular form of the lymph follicles in some lymph nodes. We are so in the habit of regarding the follicles as spherical bodies that a form such as

is represented in figure 11 seems odd indeed. Strangely enough, I never noticed any condensation of the reticulum surrounding these follicles, such as is commonly present in the spherical forms, nor could I relate their form with any peculiarity of the node or the surrounding parenchyma. They seem to result from a diffuse rather than a strictly localized proliferation of lymphocytes. I am aware, to be sure, that the least-resistance theory can also be applied here and it might perhaps offer a satisfactory explanation were it not so difficult to see why the

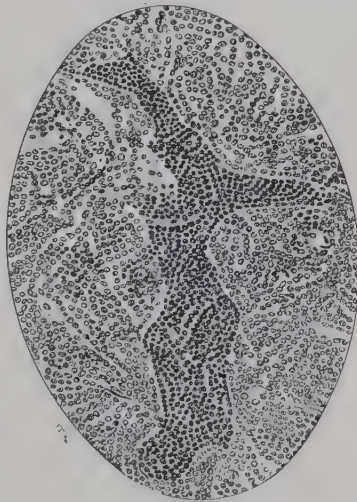


Fig. 11 A strangely-shaped lymph follicle from a lymph node of a sheep.

obstruction to growth in the various directions around an ordinary germinal center should be so nearly equal in an over-whelming number of cases of follicle formation.

The occurrence of a more or less laminated appearance due to an arrangement of the cells in more or less orderly concentric rows is also a fairly common occurrence in spherical follicles and not infrequently one meets with follicles which simulate Malpighian corpuscles very closely because of the presence of a central artery.

INTERCALATED (?) HEMAL NODES

The hemal node shown in outline in figure 12 was found in the pre-vertebral fat of a sheep. It is a very small flattened node measuring only $2.5 \times 3 \times 1.5$ mm., but is peculiar in being trans-fixed, as it were, by a vein. Although the specimen has not been examined microscopically, from what I know of hemal nodes I feel certain that it also has arterial relations and is therefore not intercalated in a vein, as the figure might suggest and as has been assumed by some. Indeed, I have never seen a hemal node solely intercalated in the course of veins, although I have seen several nodes which were completely crossed by both veins and arteries (figs. 10 and 11, "Hemolymph nodes of the sheep," Stanford University, 1913).



Fig. 12 Hemal node with two veins; actual size about 3 mm.

Since this node is so small it might seem that one of these vessels is a vein and the other a distended artery had not injections frequently shown that it is not extremely rare to find two veins leaving a single node in opposite directions. I am certain this is the case here.

THE GENESIS OF SUPERNUMERARY SPLEENS

One of the theories of the genesis of some accessory spleens has long held that they not infrequently result from the isolation of small processes or lobules from the main mass. The main and

supernumerary spleens shown in figure 13 very likely had such an origin. The specimen taken from a cat is interesting in that it shows a small narrow splenic process extending out from the parent mass, with a vessel running from the latter to the small nodular supernumerary spleen lying several millimeters distant. The main spleen was entirely normal in size and appearance and one can scarcely doubt that in this case mechanical factors were responsible for the isolation of the small splenic nodule and that hence it represents the former distal extremity of the process and is consequently a true daughter spleen. Serial sections of the latter show a wholly normal and typical splenic structure.



Fig. 13 Mother and daughter spleens from the cat; actual size of daughter spleen 2×1.5 mm.

DEPLETED HEMAL NODES

1. *Parathymic node of Ovis aries*

Some years since, while incidently interested in the occurrence of accessory parathyroid and parathymic glands in sheep, I observed that small hemal nodes were especially frequent near the parathymus glands (The parathymus glands of the sheep, *Anatomical Record*, volume 1, 1905). These nodes, which measured only a few millimeters in diameter, could not be distinguished from the *isolated* parathymus glands with the unaided eye, and were frequently found upon microscopic examination to contain very little lymphatic tissue. Some of them were indeed mere sacs of blood containing small islands or chains of

islands of lymphatic tissue. Sometimes, as in the case of the node a cross-section of which is shown in figure 14, the capsule was extremely thin. This particular node was taken from a young sheep only seven months old, but similar specimens were found in much younger and older animals.

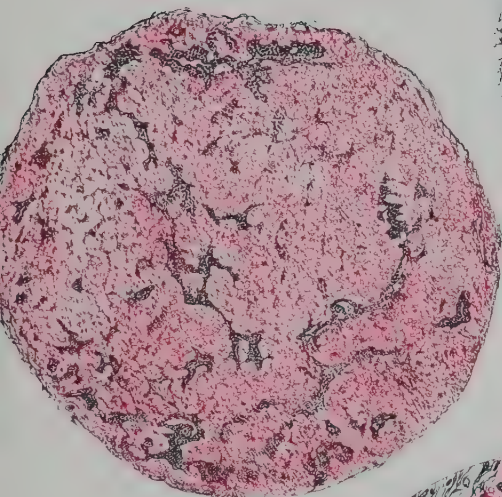
2. Paraparotid node from a newborn pig, Sus domestica

My attention was called to this specimen (fig. 15) some years since by Professor Sabin, through whose courtesy I am enabled to refer to it here. The structure of this node, which measured only a fraction of a millimeter, is entirely comparable to that above, obtained from the sheep, except that it is still more depleted of lymphatic tissue. However a careful scrutiny of the wholly depleted areas of the node from the sheep, by means of high magnification, reveals only very slight differences. Indeed, except for the specific and age differences there may be said to be distinctions between these nodes.

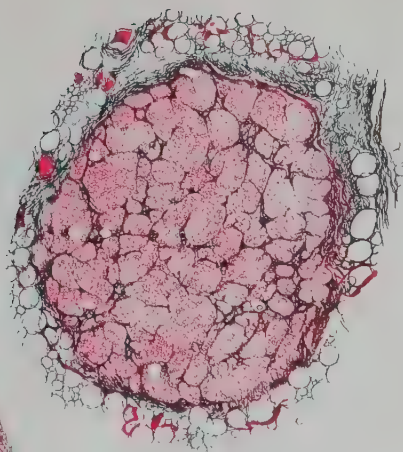
3. Node from the gastro-hepatic omentum of a colt, Equus caballus

This specimen was the only hemal node found during a careful inspection of the thoracic and abdominal cavities, of the cervical axillary and abdomino-inguinal regions of three approximately full-term colts, which material I owe to the courtesy of my colleague, Professor Jenkins. The node was $5 \times 3 \times 2$ mm. in size, intensely dark red and lay among pink lymph nodes in the gastro-hepatic omentum. As figure 16 (giving the appearance of a portion under high magnification) shows, there is far greater depletion of the lymphatic parenchyma in this node than in that from the sheep. The node is in fact merely a sac of blood-cells like that from the parotid region of the pig.

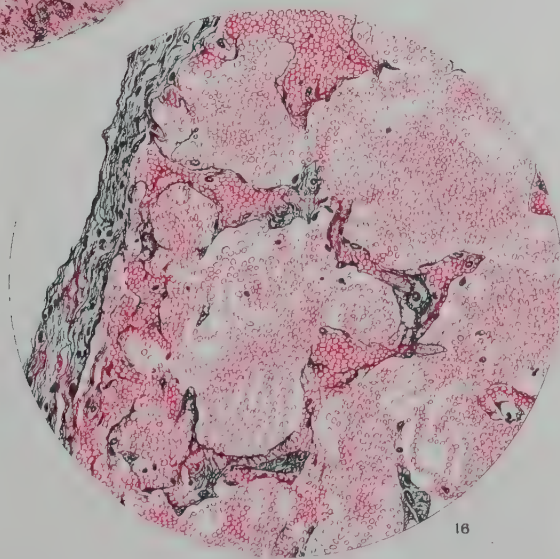
It seems decidedly interesting to me that nodes from such different species and regions, of such different sizes, and from animals of different ages, should have so similar a structure. A comparison of these with hemal and splenic nodes, represented and described elsewhere, will also show that small areas from



14



15



16

Fig. 14 Depleted hemal node from a lamb. $\times 54$.

Fig. 15 Depleted hemal node from a newborn pig. $\times 42$.

Fig. 16 Depleted hemal node from a colt. $\times 275$.

such haemal and splenic nodules from cats, dogs, sheep, bovines, goats, horses and pigs are found to have a very similar and wholly comparable structure. Indeed, were it not for specific cellular differences, we could with considerable justice speak of an identical structure.

The node from the sheep has a very thin capsule, while those from the pig and horse have relatively thick capsules, in some places at least. But since the variations in thickness of the capsules of hemal nodes and supernumerary spleens from the same animal are subject to wider fluctuations, this matter is evidently of no great significance in the differentiation of nodes. The node from the sheep also contains lacunae and vessels within the lymphatic tissue which contain disintegration products of erythrocytes, but these may be present merely because this node represents an earlier stage in a process of disappearance or appearance. Personally, I feel quite convinced that whether found in fetal or adult material, these are decadent nodes, although I am wholly open to conviction and do not urge my own conclusion.

The mention of splenic nodules in this connection is heterodox, no doubt, at least if the term splenic is to imply the origin rather than the characteristics of nodes. I would not expect a spleen to develop anywhere, but neither would I conclude that all spleen-like nodules had their origin in the splenic anlage or the main spleen itself and are hence daughter spleens. Moreover, until we are better informed upon the origin of hemal nodes and supernumerary spleens a definite conclusion would seem to be quite unjustifiable.

PANCREATIC SPLEENS IN RABBITS

The occurrence of spleen-like nodules in the pancreas of cats and rabbits was recorded elsewhere (Meyer '14). Some of these nodules are completely and others only partly imbedded in the pancreatic tissue and vary in size from those barely visible to the naked eye to others three or more millimeters in diameter. Some of these intra-pancreatic spleens have no capsule what-

soever and are surrounded by pancreatic tissue, except where in contact with the capsule of the spleen itself. Others have a distinct capsule of their own. Some of these nodules contain very small amounts of erythrocytes, while others at first sight look like mere hemorrhages. They may contain lymph follicles or typical Malpighian corpuscles or may be composed mainly of a diffuse mass of lymphocytes. There may be no trabeculae, or large ones may be present. Phagocytosis was never noticed and so far I have found these pancreatic splenic nodes in cats and rabbits only.

Figure 17 gives the appearance of one of the smaller splenic islands found in the pancreas of a rabbit. A capsule is absent in this portion; only one lymph follicle is present and islands of pancreatic alveoli surround and extend into the splenic island. The latter contains little supporting tissue and is composed almost exclusively of lymphocytes and erythrocytes, including capillaries and vessels.

A small section of another nodule is shown under higher magnification in figure 18. The definite capsule, with its serous envelope and a capillary near the periphery of the node, are very evident.

The fate of the uncapsulated splenic islands is a matter upon which I can offer no evidence, although it hardly seems that they can become and remain permanent constituents of the mature pancreas. Their presence to be sure, is easily accounted for from a developmental standpoint and it is possible that their apparent greater frequency in some animals is due to specific differences in the times, or rates even, of development of the spleen and pancreas. These cases of supernumerary spleens recall the case of Rokitsansky of a spleen in the *head* and of Kolb in the *tail* of the pancreas. The extremely interesting cases of Sneath ('13) of a scrotal spleen and of de Tyssieu ('14) of an intra-hepatic spleen also suggest that supernumerary spleens may apparently occur anywhere in the peritoneal cavity, although I presume one would be justified in a certain amount of scepticism regarding the identity of apparently splenic structures.

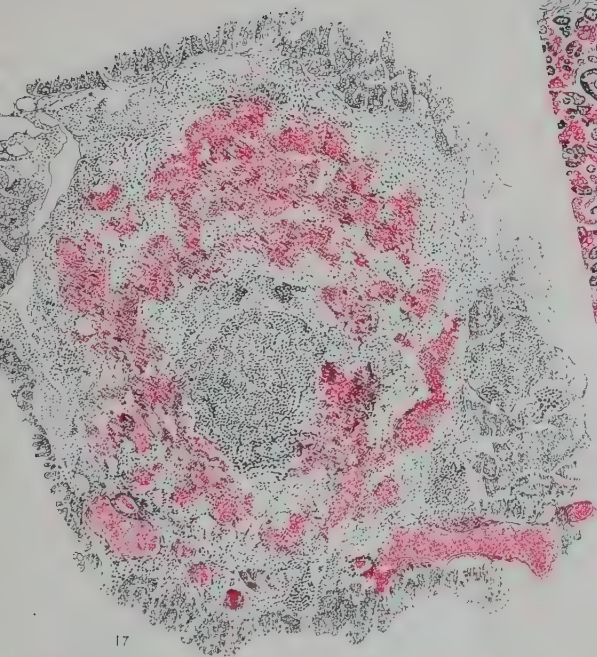
PIGMENTED 'HEMOLYMPH' NODES

As stated previously, the occurrence of pigment in hemal nodes is a comparatively rare thing. It is common, however, in hemorrhagic lymph nodes. Some of the latter are literally crammed full of light golden and brassy pigment and some darker pigment may also be present. Most of the pigment in hemal nodes is usually extra-cellular, although phagocytosis is very evident.

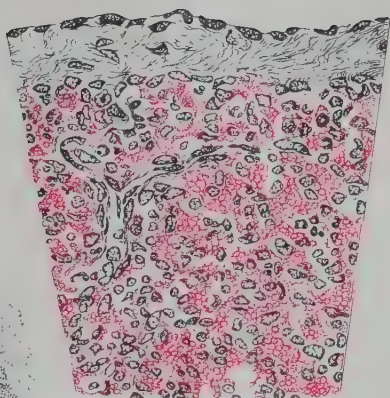
Figure 19 shows a highly magnified portion of a node, the identity of which may be open to question. This node, which was 4 to 5 mm. in size, was removed from the abdominal cavity of a sheep. It is characterized especially by the presence of sinuous masses of intensely black pigment which suggests India ink. In fact, upon cursory examination one might suppose this section to come from a hemal node which had been injected with India ink (cf. fig. 5, *The hemolymph nodes of the sheep*," Stanford University, 1914). But this is not an injected specimen at all, and the great mass of the black pigment granules in certain areas lie in capillaries in the lymphatic parenchyma. It is this gorging of the capillaries with black pigment granules which makes it simulate an injection. Nevertheless, large quantities of pigment granules are scattered about among the erythrocytes and accumulations of bright yellow pigment are also seen outside of the capillaries. Very little phagocytosis is visible in the sections of this node and the pigment gives one the impression that it is adherent to or even imbedded in the walls of the capillaries.

'MIXED' HEMOLYMPH NODES

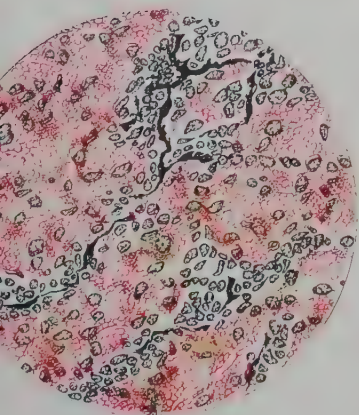
The portion of a section of the node in figure 20 shows an intra-capillary arrangement of black pigment entirely comparable to that in the previous specimen. In this specimen, however, no yellowish pigment is present and the capillaries are much more perfectly outlined by the contained pigment. Since this node, which was taken from the axillary region of a lamb, was also injected, it is evident that very large quantities



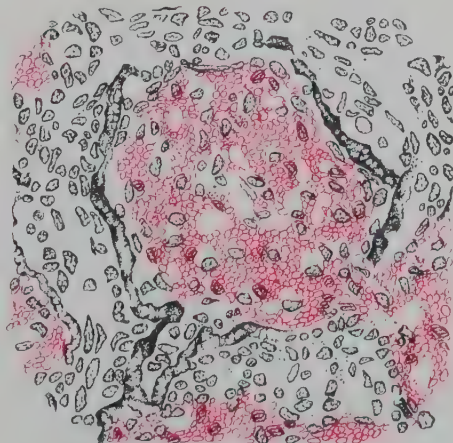
17



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19



20

Fig. 17 Pancreatic accessory spleen from a rabbit. Camera lucida. $\times 79$.

Fig. 18 Section of a pancreatic spleen from a rabbit. $\times 410$.

Fig. 19 Pigmented hemal (?) node. $\times 515$.

Fig. 20 Pigmented mixed node. $\times 515$.

of pigment must either have been formed within the node or been transported there. The capillaries are outlined in this manner by the black pigment throughout practically this whole large node. There are also loose pigment granules in abundance in the parenchyma but there is little evidence of phagocytosis. This node was obtained from an animal five and a half weeks old, which was killed by bleeding. Forty to fifty small hemal nodes were found in the abdominal cavity. None of these nodes were in connection with the mesenteric lymphatics although many of the lacteals which were engorged with chyle—the lamb had nursed before killing—ran about and over hemal nodes both within and at the root of the mesentery.

Many pigmented and pink nodes that were injected were found to be lymph nodes. But in the left subscapular region a large dark red node, 1 cm. in size and flattened latero-medially, was found. Except for the disposition of the vessels this node looked like a hemal node and seemed to be a mere sac of blood. It was located at the bifurcation of the subscapular vein lying between the dorsal and ventral branches. Since it was so large it was injected with India ink and as I had never found a true hemal node in this region the result of the injection did not wholly surprise me. The India ink quickly entered typical afferent lymphatic vessels, which ran to reddish nodes which lay along the course of the axillary vessels. The nearest of these axillary nodes was 4 to 5 cm. distant and the injection could be followed from node to node to the jugulo-subclavian junction. The result of the injection then would seem to indicate that this dark red node was, after all, a typical lymph node.

An anomalous result of the injection was the fact that some of the India ink easily and quickly found its way into the dorsal branch of the subscapular vein. Indeed, so much of the ink entered the axillary vein from here that some of it was later recovered from this vein by means of filter paper and identified as such. This ink had entered the axillary vein from the branch of the subscapular, which was connected with the node by a small vessel which clasped the node after the manner of the afferent lymphatics but which was filled with blood before

injection. The efferent vessel, which was also filled with blood, likewise arose by numerous branches which clasped the opposite sides of the node as they emerged from it so that the branches from these two vessels practically clasped the whole node from opposite sides.

Upon examining the right axillary and subscapular regions, a node apparently identical in all respects with that found on the left side was found in exactly the same location. Careful inspection showed that the large vessel leaving the node, which was also engorged with blood, had the typically beaded appearance of lymphatic vessels. Had it contained lymph instead of blood no one would have questioned its lymphatic character.

The short trunk (0.5 cm. long), which was formed by a number of clasping branches which emerged from the node and entered the dorsal branch of the subscapular vein, was filled with blood and also had the appearance of the short vessel in the previous specimen. This node was excised and imbedded in celloidin; figure 20 was made from a portion of a section.

The gross appearance of both nodes and the results of the injection of that on the left side seem to indicate that both these nodes were undoubtedly in communication with the subscapular vein by means of a short vessel, the branches—or radicles—of which embraced the node, and that they were also in communication with axillary and cervical lymph nodes by means of a vessel which had the form and characteristic of a lymph vessel.

That the India ink entered the subscapular vein without the least obstruction and without the least distension of the node is good evidence that the internal architecture of the node was not unduly disturbed. Those familiar with the history of the injection of the lymphatic system will no doubt be reminded immediately of the similar results obtained by the early experimenters—especially by those using mercury. Nevertheless, even the authority of such great names as those of Haller, Mascagin and Sömmering, not to mention Cruikshank, regarding lymphatico-venous communications, has been compelled in the course of time to yield to the higher authority of facts.

Even if the observations of Fohmann, Lauth and Panizza, on the occasional termination of the lymphatics in the femoral and iliac veins of birds, and the similar observations of J. Müller on amphibia and of Fohmann on the latter and on swine, remained unconfirmed, no one could disregard the recent observations of Baum, Huntington, McClure and Sylvester, made in connection with modern methods. Besides, there are the early anomalous cases in human cadavers of Conring, Duvernoy, Kaaw, Kulmus, Hebenstreit, Mertrud, and also the interesting observation of Wutzer, which was confirmed at the time by J. Müller.

Hence, it seems to me that one can hardly doubt that these two nodes really were connected with the subscapular veins in such a manner that the venous current was shunted through them and then passed through the efferent lymphatics, thus coloring the intermediate lymph vessels and nodes pink. Had there not been two nodes on opposite sides of the body, with wholly similar characteristics, one might have assumed that the point of the needle had damaged the internal architecture in such a way as to let the blood enter both a lymphatic space and a venous radicle. But even such an assumption does not explain the characteristics of the nodes before injection.

The specimen which was sectioned is completely filled with blood and lymphatic tissue. Lymph sinuses are nowhere visible, and erythrocytes and lymphocytes are intermingled except in those portions of the lymphatic parenchyma which are extended throughout the node like large trabecula, or in areas in which there are many follicles and very little blood.

Designating these nodes as 'lusus naturae' does not, to be sure, explain their presence, nor does the rare occurrence of such specimens justify one in regarding them as being representatives of a separate type of node. Nor are they the exceptions which prove the rule, although they help very materially in establishing the occurrence of atypical lymph and hemal nodes and in explaining occasional anomalous results obtained by injections of lymph nodes, as already emphasized.

DIAPHRAGMATIC LYMPH NODE IN A RABBIT

This node, which measured $4 \times 3 \times 2.5$ cm., was located on the central tendon of the diaphragm, ventral to the vena cava. It lay partly on the tendon and partly on the diaphragmatic musculature and projected into the abdominal cavity. It had the appearance of a lymph node but no lymph vessels were seen in its neighborhood. Upon microscopical examination it was found to be provided with a very evident but ill-defined capsule.

It is a very vascular node, contains no evident lymph sinuses but some coagulum which looks like lymph and also several degenerated areas of considerable size. Some of the parenchyma is quite definitely arranged in cords. Degenerated erythrocytes and a few pseudo-polykaryocytes are also present. Since the rabbit had been treated with goat serum it is of course possible that the areas of degeneration were partly or wholly, due to these injections. There was also an excess of serous fluid in the peritoneal cavity.

INTRA-GLUTEAL BURSA

Two large subcutaneous bursae were found symmetrically placed in the gluteal region of the female cadaver. They were empty and measured 5 cm. in depth and 2 cm. in width. Both were located in the medial margins of the glutei maximi muscles, directly beyond the lateral margins of the ischio-rectal fossae. The skin over them was wholly normal in appearance and they were partly contained in the subcutaneous fat of these regions. The far larger portion of each, however, was contained in the glutei. These bursae were in no sense comparable in location to the ordinary subcutaneous bursae and could with entire justice be designated as intra-muscular. Their walls were very thin and smooth and contained no evidences whatever of having had an inflammatory origin. Since their genesis in this location would be a matter of pure surmise it seems futile to speculate.

AN ANOMALOUS VAGO-SYMPATHETIC PLEXUS

Since comparatively few students do a sufficiently careful dissection adequately to reveal the sympathetic system, our knowledge of variations and developmental defects of the autonomic system lags far behind that of other systems. Furthermore, the descriptions in our textbooks are rather inadequate. In addition to greater skill and time on part of the student, a searching supervision on part of the instructor is also necessary to reveal the many variations. Besides, not everyone can be specially interested in the sympathetic system; I, for one, confess to having given it scant attention.

Both the right vagus and sympathetic are normal in the cervical region of this subject except that the vagus passes dorsal to the subclavian artery. The superior cervical ganglion is large and the middle and inferior ganglia are 1 cm. apart and are joined by two trunks. The lateral trunk of this joining loop gives off a branch 1 cm. long, which forms an annulus vertebralis instead of an annulus subclavii, as is not infrequently the case.¹ A fairly well-defined ganglion marks the point where the annulus vertebralis begins to form. From the latter several branches are given off and from the dorsal trunk of the annulus numerous branches extend to the common carotid, subclavian and innominate arteries. The two subdivisions of the sympathetic join directly after forming the annulus, and join the first thoracic ganglion. The latter is well-defined, although somewhat elongated, and the rest of the right sympathetic chain is normal.

About 1.5 cm. caudal to the inferior cervical ganglion of the sympathetic another somewhat stellate ganglion, about 4 mm. in size, is located. This ganglion was joined by the recurrent laryngeal branch of the vagus, which was rather small. The recurrent branch is not merely enclosed in the same sheath but definitely forms a ganglion with the sympathetic at the point of union. A somewhat larger branch than the pre-ganglionic branch of the vagus leaves this ganglion to form the inferior

¹ I have seen an annulus innominatus but once.

laryngeal nerve, which is accompanied by a tracheal and several esophageal branches.

Three parallel branches about 1 mm. in caliber leave the caudal portion of the ganglion and join with several similar though somewhat smaller branches, which arise from the caudal end of the dorsal arm of the annulus vertebralis to form the right pulmonary plexus; these branches are about 3 cm. long. The accompanying diagram, figure 21, illustrates these anatomical relations as found in the cadaver of a white female.

TRAJECTORIAL STRUCTURE IN THE SACRUM

Since it will always remain an impossibility mathematically to prove the existence of trajectorial structures in the spongiosa of

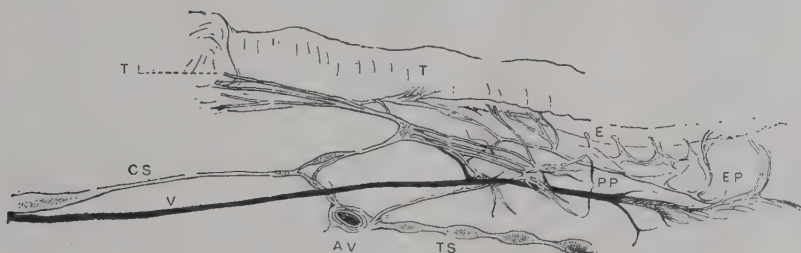


Fig. 21 An unusual vago-sympathetic plexus.

bones, their presence here and there must always remain a matter of opinion, even if not of conjecture. Although mathematical proof of the existence of such an architecture must remain impossible because of the indeterminable character and the complexity of the acting forces, a more careful examination will probably reveal the presence of such an architecture in some locations heretofore undescribed. Indeed, until the whole human skeleton has received as careful an examination as some of the bones, it is highly probable that we shall also remain ignorant of many decidedly interesting variations in the spongiosa architecture, even if not of the prevailing fundamental structural types.

During an inspection of a series of sections of laboratory remnants, my attention was attracted to some sagittal sections of sacra made in the ordinary dissecting-room routine. One of the things noticed was a prominent spur of compacta, which extended dorsally from a mid-point on the ventral surface of some of the bodies of the sacral vertebra (fig. 22). These spurs or bars, which reinforced the ventral portions of the individual sacral vertebra, were not infrequently porous and looked as though they were in a process of dorsal extension. The portions of the spurs which were not porous were extremely firm and hard, and in fact looked eburnated. None was ever found in the first sacral vertebra. In short sacra they seemed to be commonest in the bodies of the second and third, and in long sacra in the third and fourth, sacral vertebrae; they were never observed in straight sacra. Not infrequently the compacta was slightly thickened opposite the mid-points of these vertebrae and when the spurs were absent the thickening often was located at the bottom of a depression in the middle of the ventral surface.

But a more striking thing still was the existence of a very evident trabeculated disposition of the spongiosa in the third and fourth and less frequently also in the more distal sacral vertebrae. This architecture was very definite and very similar in all cases where it was evident. As indicated in figures 22 and 23, the main trabeculae were perpendicular to the ventral surface at its mid-point but there were also oblique trabeculae on either side. Other smaller and less evident trabeculae extended approximately at right angles to these.

Since such a disposition of the spongiosa was not present in all sacra examined, one is naturally tempted to speculate. But it is likely wise to defer any possible explanation until a more extensive survey can be made. It is clear, however, that the thickening of the ventral compacta, the occurrence of spurs and the peculiar disposition of the spongiosa here described, are all admirably adapted to resist the tendency of body weight in sitting and of muscle pull from breaking particularly the middle and also the lower sacral vertebrae by ventral flexion.

The illustrations are a faithful representation of the originals, though they show the characteristic architecture somewhat inadequately. From an examination of these drawings it will be evident how well-adapted such an architecture is to withstand the effect of the forces that must be active in every sacrum, even if they are not equal in magnitude or in direction.



Figs. 22-23 Sagittal sections of portion and entire human sacra, showing spurs and trajectories.

THE MOLDING EFFECT OF MUSCLE PRESSURE

Attention was called in another connection, to the effect of tendon pressures in affecting, even if not in determining, the relief of bones. The following three specimens of humeri—two of which I owe to the courtesy of my colleague, Professor Ophüls—seem to show the effects of muscle pressure and tension

in a striking way. In the left humerus, shown in figure 24 *a*, the whole greater tuberosity, which is decidedly enlarged by the deposit of much additional bone as a result of periostitis, is literally drawn out in the direction of pull of the spinatus and teres minor muscles. In fact, the whole bony mass looks as though it had been pulled in this direction while in a viscous condition.

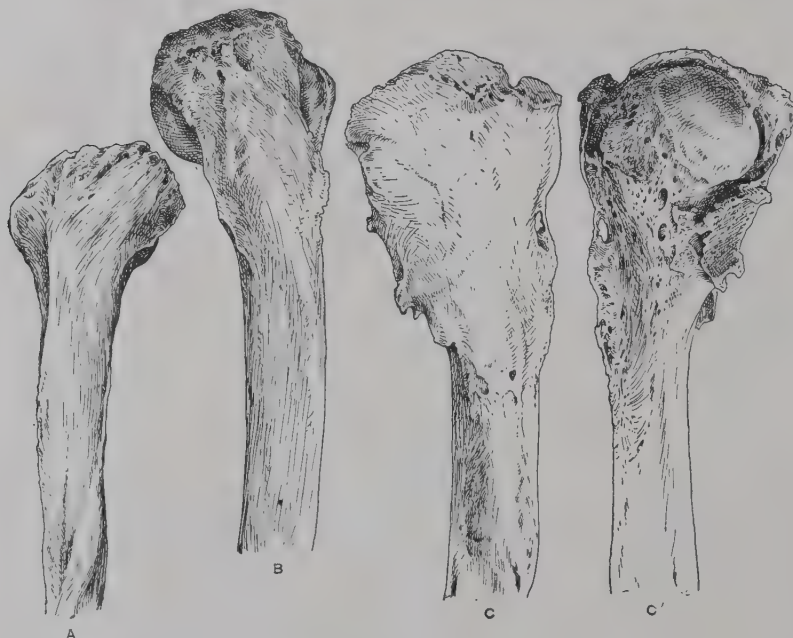


Fig. 24 Humeri showing the molding effect of muscle pull and pressure.

The lesser tuberosity and the rest of the bone are practically normal save for very slight evidences of arthritis. Aside from the slight arthritis there was nothing about the rest of the skeleton or the cadaver which suggested an explanation for this peculiarity of the greater tuberosity.

The other two humeri, shown in figure 24 *b* and *c*, were isolated specimens. The greater tuberosity of the right humerus, *b*, shows a peculiarity similar to *a*, but the deposit of new bone is

far greater in extent, and the proximal portion of the shaft of the humerus immediately distal to the head is bent medially. The humeral head and the whole lateral surface of the proximal part of the shaft are also flattened and new bone has been deposited along both tubercular ridges and on the medial side of the surgical neck; the rest of the bone is normal.

In addition to the dragging dorsally of the greater tuberosity, distinct flattening and molding of the lateral surface of the proximal portion of the shaft and of the new bone are plainly evident. This molded surface is also marked by very fine sulci, which suggest arterial impressions. Even delicate anastomoses of fine sulci are present and quite a complete network is evident under slight magnification with a reading-glass.

The tuberosities of the third specimen—the right humerus, *c* and *c'*—are in the normal location and the greater tuberosity was but slightly affected by the disease. The intertubercular sulcus is quite normal but is roofed over very largely by a thin layer of bone, which is part of the large thin mass of new bone deposited on the proximal portion of the humeral shaft. This thin mantle of new bone rises above the lesser tuberosity and hoods it and the humeral head. The outer surface of the new bone shows a canalization similar to that in the previous specimen, but it is more complete and shows sulci made by larger vessels. The molding effect of the deltoid on this new bone, is so unmistakable that a mere glance suffices to reveal it.

Since the lateral portion of the humeral head is capped by the new bone it could have articulated with a portion of the glenoid fossa only. The rest of the humeral shaft is practically normal.

An explanation of the observations recorded here seems quite impossible in the entire absence of a clinical history. Arthritic deposits rarely show such very evident molding and since the dragging dorsally of the greater tuberosity, especially in the first specimen, is not limited to the new bone, one is tempted to assume that these humeri must have been fairly plastic at some time. But the condition of the rest of the bones does not confirm such a supposition and I do not see how a greater plasticity could be confined to such a small area.

FREELY ENDING CAPILLARIES IN HEMAL NODES

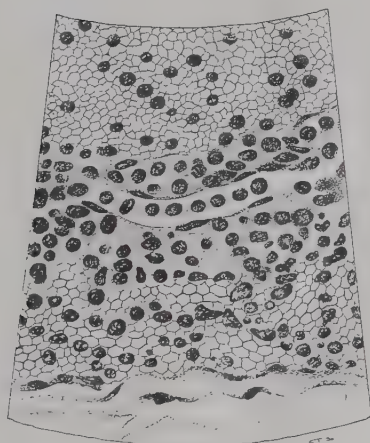
I have elsewhere expressed the opinion that capillaries in non-depleted hemal nodes communicate directly with the venous lacunae. The main reasons for coming to this conclusion were that the results of injections into the vena cava and aorta in lambs gave entirely comparable results and that capillaries could not be seen ending freely within the parenchyma of the nodes. In case of the injections the injected mass of ink could never be seen in a freely ending capillary and was always found in the venous lacunae.

In figure 25 a section of a capillary is shown, containing a number of leucocytes arranged in a row within the capillary and also several beyond the mouth of the capillary, similarly arranged. This drawing was made with an oil immersion lens and the specimen would seem to represent leucocytes either entering the free end of the capillary or passing through a gap in its wall.

It is the only specimen I have found in a careful study of many many sections indeed and has been in my possession for some years. I report it here with some indifference since it is of questionable value. A somewhat similar arrangement of erythrocytes near a real gap in the wall of a venous lacuna, is a much more frequent thing, however, and this and other observations seem to suggest that such gaps in the walls of the lacunae occur normally in hemal nodes.

HEARTS WITH BIFID APICES

As reported and fully set forth by Mall ('12) and the literature cited by him, hearts showing more or less of an indentation at the apex are not very rare. The two hearts shown in outline in figures 26 and 27 possess this characteristic to a varying extent, the bifurcation in that shown in figure 27, being very marked. This notch between the apices of the right and left ventricles was also much more evident at autopsy and is deeper than an outline of the exterior indicates. This heart, which was obtained from the body of a white man who had fasted absolutely for sixty days, was quite flabby and probably for



25



26



27

Fig. 25 Freely ending capillary in a hemal node of the sheep. $\times 1050$.

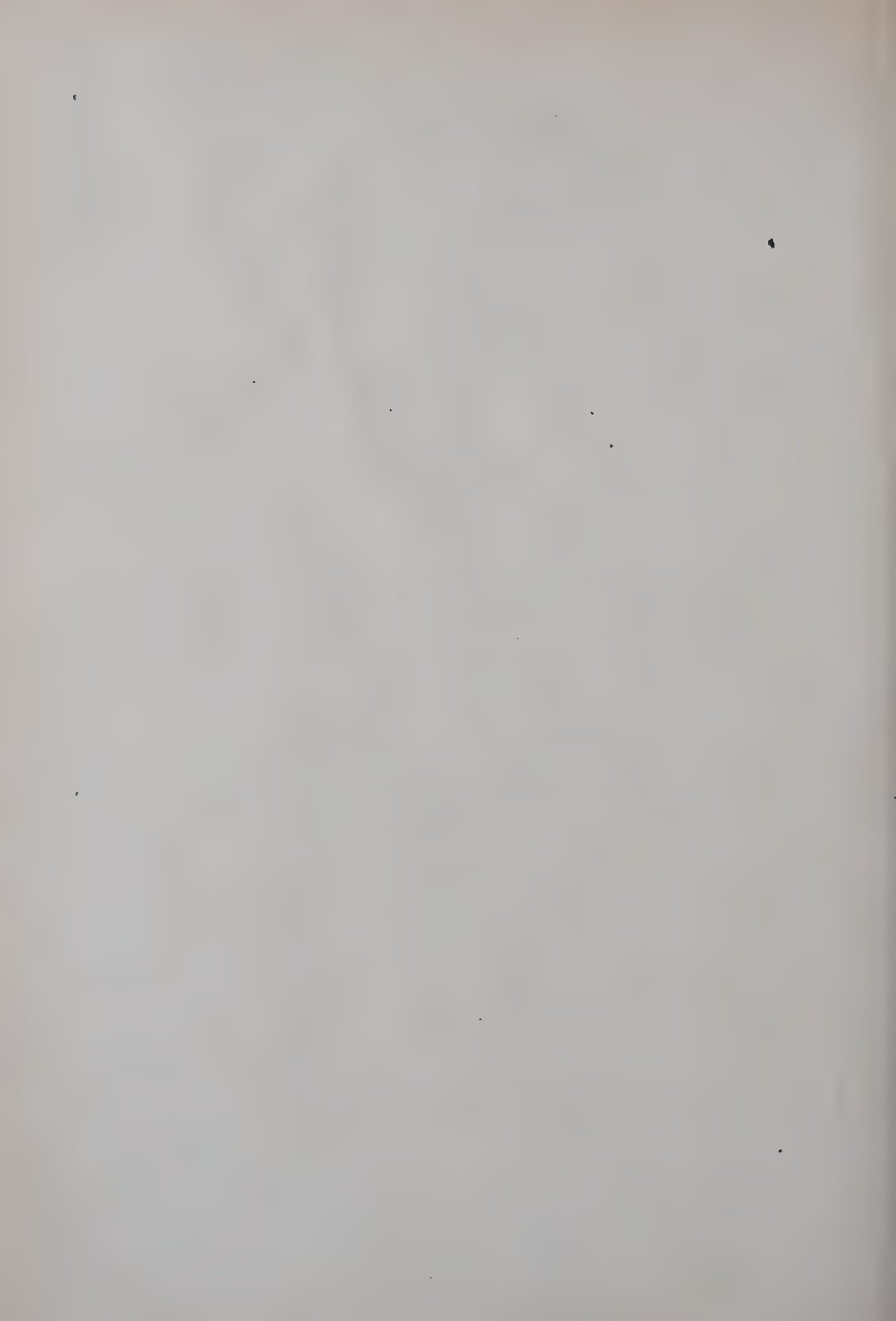
Figs. 26-27 Human hearts with bifid apices; half natural size.

this reason the tip of the right ventricle was turned laterally so that the gap between the two apices was wide. The specimen is otherwise normal. Since Mall ('12) explained this anomaly fully, further comment is unnecessary here.

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EXPERIMENTAL STUDIES AIMING AT THE CONTROL OF DEFECTIVE AND MONSTROUS DEVELOPMENT¹

A SURVEY OF RECORDED MONSTROSITIES WITH SPECIAL ATTENTION TO THE OPHTHALMIC DEFECTS

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TWENTY-NINE FIGURES

INTRODUCTION.

The problem of the causes underlying defective development has recently received very exhaustive and illuminating treatment by Mall ('08). Basing his conclusions on his own study of 163 pathological human ova and on recent results of work in experimental embryology, he suggests that the human monsters are—with the exception of the hereditary 'merosomatous' terata—due to injurious influences of atypical environmental factors. He makes the specific suggestion—which seems justified in the light of evidence brought forth by him as well as by clinical data—that the monstrous development of some ova may be due to their inadequate nutrition owing to the imperfect implantation in a diseased uterus. It would seem that this hypothesis may hold good at least for some pathological embryos aborted during the first two months of pregnancy. It is obvious, however, that Mall's interpretation could not be extended to monstrous fetuses of the later months of pregnancy or to monsters after full-term birth; for an ovum suffering from lack

¹ This contribution is based on a paper read by title ("Is defective and monstrous development due to parental metabolic toxemia?") at the meeting of the American Association of Anatomists held at St. Louis, December 29, 30, 1914. *Anat. Rec.*, vol. 9, no. 1, pp. 133-137.

of nutrition could not well be imagined to live on to these later stages of development.

Some environmental factors must be looked for other than faulty implantation of the ovum, to account for the occurrence of such cases. The results of investigations in experimental embryology and teratology by Dareste ('91), Roux ('95), Hertwig ('96, '10), Féré ('94), Morgan ('02, '04) Stockard ('07, '09) and others, who obtained monstrous development of ova which had been subjected to the action of physical or chemical modifications of the environment, suggested to me that the human as well as the other mammalian monsters may be due to the physical or chemical action of some substances in the blood of one of the parents on either one of the sex cells or on the fertilized ovum, respectively.

Stockard ('09) has expressed the unsupported view that cyclopia in man may possibly be due to an excess of magnesium salts in the blood of the mother, and in later publications ('10 b), concluding from his experiments with alcohol solutions, he suggests that the cyclopean defect might perhaps be attributed to alcoholism of either one of the parents. It is rather evident that this latter assumption may be regarded as justified only for a negligibly small percentage of monsters. For such defects are not infrequently found in mammals as well as in other vertebrates where the possibility of alcoholism is entirely eliminated. The solution of this problem appeared to me to be elsewhere. Since the metabolism is the main source to which chemical modification of the body might be traced, I concluded that the toxic substances found in the blood of individuals afflicted with some metabolic disturbances might be the ones which could be made responsible for the origin of monstrous development.

MATERIAL AND METHODS

To test the validity of this hypothesis it would be necessary to produce experimentally in mammals such disturbances of metabolism as diabetes, nephritis, jaundice, etc., to mate thus diseased animals and eventually to study the heredity of such offspring as they may beget. Such experiments, however, are

difficult to perform in the absence of certain facilities, which are not usually accessible to the biologist. On the other hand, the spontaneous occurrence of these diseases in animals is too rare to permit of conclusive breeding experiments. It was necessary, therefore, to confine myself to a preliminary step in the investigation. This consisted in subjecting eggs of an oviparous vertebrate to the action of some toxic substances found in the urine under certain pathological conditions of metabolism.

The eggs of *Fundulus heteroclitus* were chosen, and after being fertilized they were exposed in early (1 to 2, 2 to 4, or 4 to 8, and 8 to 16, cells respectively) cleavage stages to the influence of solutions in sea-water of such substances as urea, butyric acid, lactic acid, acetone, sodium glycocholate, ammonium hydroxide, etc. Only with two of these substances, viz., butyric acid and acetone, have so far definite and positive results been obtained.

In the case of butyric acid, 10 cc. of a $\frac{1}{12}$ to $\frac{1}{4}$ gram molecular solution in 50 cc. of sea-water was found to be approximately the optimal solution, i.e., causing the greatest number of eggs to develop in a defective manner. If fertilized *Fundulus* eggs were left in this solution for fifteen to twenty hours and afterwards transferred to pure sea-water a great number of them gave rise to monsters. Similar results were obtained with solutions of acetone. Here the eggs were exposed in a number of dishes to the action of solutions of 20, 25, 30, 35, 40, 45 and 50 cc. of a gram molecular solution of acetone added to 50 cc. of sea-water. A varying relative number of deformed embryos was found in all dishes, increasing with the strength of the solution up to 40 cc. of acetone and decreasing in solutions still stronger, which caused an increase in the death-rate of the eggs. The length of exposure to the action of acetone was forty-eight hours in most and twenty-four and seventy-two hours respectively in some experiments. It was found that while long exposures increased the mortality of the eggs the difference in effect on the surviving eggs was very slight between exposures of twenty-four and those of forty-eight or even seventy-two hours. This points to the probability that it is mainly the initial effect

of the toxic solution on the ovum that causes it to develop in an atypical manner. The eggs were fixed and preserved after Child's sublimate-acetic-formaline method and were left in 4 per cent formaldehyde until the time of their imbedding. They were imbedded in celloidin-paraffin, chloroform being used as a clearing agent. Sections were cut 6 or 7 μ thick, stained with Delafield's hematoxyline and counterstained with erythrosin.

SURVEY OF THE MORPHOLOGICAL RESULTS

1. Deformities of the sense organs and the mouth

The morphological results obtained in both series of experiments, with butyric acid and acetone, being very much alike, it will suffice to state that the deformities enumerated here were found to be common to both. Great numbers of cyclopean embryos were found in both these series of experiments. I have recorded in my observations the occurrence of transition from two normal eyes in the typical position in the head all the way down through the more or less closely approximated eyes or eyes of a double composition and true cyclopia to complete anophthalmia (figs. 1-7) as described by Stockard ('09) in his experiments with magnesium chloride and alcohol, and by Lewis ('09) in his pricking experiments. Other defects in the development of the eyes such as asymmetric monophthalmia (fig. 8) and microphthalmia (fig. 9) were also found to occur abundantly. In some embryos all that could be detected of the eyes were lenses only or a rudiment of the choroid coat with or without a rudimentary lens. Coloboma, by which is understood a patency of the embryonic fissures of some parts of the eye, was found in some cyclopean as well as in two eyed but otherwise defective embryos.

Stockard ('09) has also described a peculiar change in the form and position of the mouth of the cyclopean embryo. The mouth in such embryos has the appearance of a snout, a proboscis-like structure, and is pushed down below the cyclopean eye. This displacement into the ventrolateral position Stock-



Figs. 1-29 Sketches of monstrous *Fundulus* embryos.

Fig. 1 Normal *Fundulus* embryo, twelve days old, to show the position of the eyes; *h.*, heart.

Fig. 2 *Synophtalmia bilentica*, from $\frac{1}{16}$ gram molecular butyric acid, eighteen days old.

Fig. 3 *Synophtalmia bilentica*, from $\frac{1}{12}$ gram molecular butyric acid, twenty-eight days old, with 'proboscis'-mouth, *m.*

Fig. 4 *Synophtalmia bilentica*, from $\frac{1}{12}$ gram molecular butyric acid, twenty-eight days old.

Fig. 5 *Synophtalmia unilentica*, from $\frac{1}{12}$ gram molecular butyric acid, twenty-four days old.

Fig. 6 Cyclopean embryo, showing one unusually large median eye with fused olfactory pits, *o.p.*, and proboscis-like mouth, *m.* From $\frac{1}{12}$ gram molecular butyric acid, eighteen days old.

Fig. 7 Anophthalmic embryo with club-tail and distended ear vesicles, from acetone solution (40 cc. gram molec. sol. to 50 cc. sea-water), thirteen days old.

Fig. 8 Asymmetrically monophthalmic embryo, with greatly distended ear vesicles, *e.v.*, one pectoral fin only and club-tail. From acetone solution (35 cc. gram molec. sol. to 50 cc. sea-water), thirty-two days old.

ard attributes to the circumstance that the cyclopean eye being frontally located has caused the mouth to move downward. This interpretation, however, seems to be insufficient in view of the fact that I have observed in my experiments this occurrence not only in cyclopean monsters (fig. 6) but also in some cases of synophthalmia (fig. 3), asymmetric monophthalmia (fig. 8) and in many cases of dorsal microphthalmia (fig. 9). In some asymmetrically monophthalmic embryos (fig. 29) the mouth, while being apparently normal in shape, occupied the position in which normally the lacking eye would have to be located.²

Abnormalities of the olfactory pits were also almost invariably found to occur in embryos exhibiting various degrees of median 'cyclopia' (fig. 6) as well as in asymmetrically monophthalmic embryos (fig. 20). They usually corresponded to the anomalies of the eyes of a given embryo, that is, were either blended into one median pit or exhibited various degrees of approximation or fusion respectively in the cyclopean embryos. In the asymmetrically monophthalmic embryos where the mouth had taken the position of the missing eye, the nasal pit of the side possessing the eye was usually found to be in the normal position, while the pit belonging to the side lacking the eye has sometimes been found to be located posterior to the mouth. This unilateral ectopia of the nasal pit in the monophthalmic embryo is probably secondary to the ectopia of its mouth. These changes in shape and position of the mouth as well as of the olfactory pits are apparently due to processes of regulation after an blastolytic destruction of a certain area at the anterior end of the early embryo's body.

In a great many embryos the auditory vesicles reached enormous size, which on microscopic examination seemed to be due

² In a previous note ("The influence of products of pathologic metabolism of the developing teleost ovum," *Biol. Bull.*, vol. 28, no. 1, pp. 51-57), it was stated (p. 54) that in some cases of asymmetric monophthalmia an open orbit was found on the side lacking the eye. This error was made owing to the transparency of the living specimens. It was the mouth in the exact position of the eye that was mistaken for an 'open orbit.' The error was found when the drawings of the living embryos were compared with the fixed specimens.

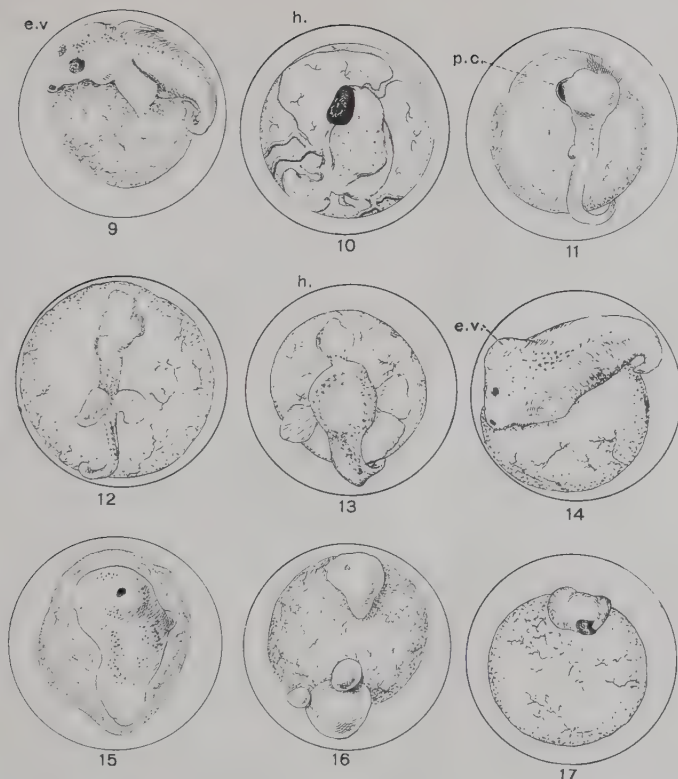


Fig. 9 Microphthalmic embryo (small eyes dorsally located), with distended ear vesicles, *e.v.*, From $\frac{1}{16}$ butyric acid, twenty-nine days old.

Fig. 10 Greatly malformed cyclopean embryo with dorsally located eye, rudimentary pectoral fins and club-tail, from $\frac{1}{12}$ gram molecular solution butyric acid, thirteen days old.

Fig. 11 Greatly malformed embryo from acetone solution (35 cc. gram molec. sol. to 50 cc. sea-water) with one rudimentary lateral eye, without fins, club-tail; *p.c.*, distended pericardial vesicle.

Fig. 12 Extremely malformed anophthalmic embryo from acetone solution (20 cc. gram. molec. sol. to 50 cc. sea-water), fourteen days old.

Fig. 13 Greatly deformed anophthalmic embryo, with head partly constricted off from the rest of the body. From acetone solution (36 cc. gram molec. sol. to 50 cc. sea-water), sixteen days old.

Fig. 14 Extremely malformed, oedematous embryo, with one rudimentary lateral eye, distended ear vesicles, *e.v.*, with club-tail and without pectoral fins. From $\frac{1}{2}$ gram molecular butyric acid, fourteen days old.

Fig. 15 Amorphous embryo from acetone solution (40 cc. gram molec. sol. to 50 cc. sea-water), sixteen days old.

Fig. 16 Egg with amorphous tissue fragments on yolk-sac, from acetone solution (30 cc. gram molec. sol. to 50 cc. sea-water), thirteen days old.

Fig. 17 Microplastic embryo with rudimentary eyes, from acetone solution (35 cc. gram molec. sol. to 50 cc. sea-water), twelve days old.

to an oedematous distension (figs. 7, 8, 9, 14). In some monophthalmic embryos which had hatched a similar observation was made to the one recorded by Stockard ('09) in his experiments. These embryos "swam in circles, often whirling around with great rapidity, much as Japanese waltzing mice do. Others swam in irregular spirals and only progressed in a straight direction with difficulty." In most of them I observed that when forced to swim in a straight forward direction they would immediately drop to the bottom of the dish, while they were able to swim for some distance along the wall of the finger-bowl in which they were kept. Stockard attributes this functional anomaly to "a defective muscular arrangement, the animal's body being slightly bent or twisted so that it is unable to straighten perfectly." From my own observations and Stockard's ('10 a) microscopic findings I am rather inclined to think that in these embryos—at least in my own experiments, if not also in those of Stockard's—the locomotor anomaly is due to defects in the semi-circular canals.

2. General defects; 'meroplastic embryos'

Besides the already referred to deformities of the sense organs there were found in both butyric acid and acetone solutions great numbers of embryos which developed in a much more defective manner, the malformation involving practically the entire bodies. Thus curiously deformed dwarfs with vestigial eyes or blind, or slender, elongate, greatly malformed embryos (fig. 11) often with waistlike constrictions (figs. 12 and 13) were of not infrequent occurrence. A considerable number of eggs were recorded with amorphous embryos (fig. 15) or only amorphous fragments of tissue (fig. 16) on the yolk-sac. The amorphous embryos would correspond in homology to those found in man and described by Mall (l.c.) and others. On microscopic examination of several amorphous embryos it was found that the nervous system, the notochord and the viscera while having developed, are highly abnormal and rudimentary in structure. The sections present pictures similar to those of

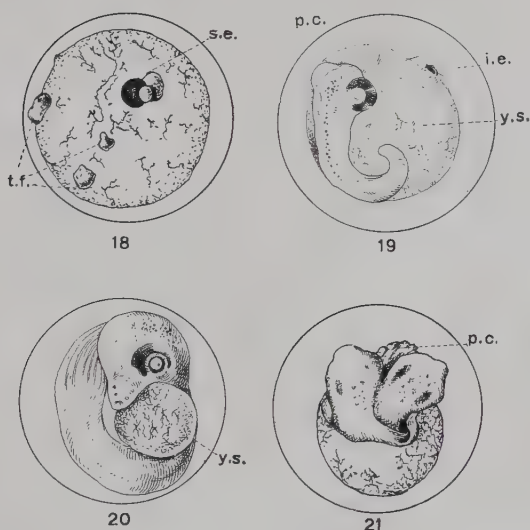


Fig. 18 Egg with 'solitary eye,' *s.e.*, and three very small clastolytic tissue fragments, *t.f.*, from acetone solution (35 cc. gram molec. to 50 cc. sea-water), twelve days old.

Fig. 19 Asymmetrically monophthalmic embryo, with club-tail, without pectoral fins. On the yolk-sac at a distance from the embryo is seen an 'isolated eye,' *i.e.* From acetone solution (40 cc. gram molec. sol. to 50 cc. sea-water), 12 days old; *p.c.*, pericardial vesicle, *y.s.*, yolk-sac.

Fig. 20 Asymmetrically monophthalmic embryo with 'proboscis'—mouth, without pectoral fins. From $\frac{1}{2}$ gram molecular butyric acid, twenty-eight days old.

Fig. 21 Duplicity anterior; both components are anophthalmic. From acetone solution (35 cc. gram molec. sol. to 50 cc. sea-water), sixteen days old.

sectioned amorphous fetuses of man. The amorphous fragments may be compared to the 'nodular forms' of Mall which he found in some aborted human ova.

By far the most numerous were found to be eggs in which only a part of the body (fig. 17) had developed—'meroplastic embryos' (Roux, l.c.). In these the hind parts of the bodies were missing to a greater or lesser extent, while the anterior parts were often extremely deformed, their shape being much distorted and only more or less rudimentary eyes being present. Many of them in

which an anterior half of the body had remained would belong to the class designated by Roux (l.c.) as 'hemibryones anteriores,' which he and subsequently other investigators found to develop from the frog's egg if one of its first two blastomeres was punctured with a hot needle.

The other cases of meroplastic development concern embryos in which either more than the anterior half of the body had developed, or less. They range all the way from those in which hardly much more than the tail was missing to those in which only a very small anterior part of the head (usually with one or sometimes with two vestigial eyes) was present.

3. Independent development of an eye from a fragment of the medullary plate

By far the most curious and most significant of all the meroplastic ova recorded in these experiments were some in which all that was left of the embryo was a fragment of brain tissue with a solitary eye. The fragment of brain tissue was in some cases somewhat larger than the solitary eye to which it has given rise, while in others it was smaller. In one of these eggs (fig. 18) in which the solitary eye was rather defective—the chorioid fissure being patent—several small amorphous fragments of tissue could be observed at different points of the yolk-sac at a considerable distance from each other. Since I have observed such fragments of tissue on many other eggs in which either a defective embryo or nothing else besides the amorphous fragments had developed, I am inclined to think that such cases give us a clue as to what processes may be involved in bringing about the effects recorded in this work.

The 'solitary eyes' when observed in the living egg had the typical appearance of eyes and no doubt could be felt that the interpretation of these sporadic cases was correct. However, as no other similar case was known, it seemed rather improbable that a small fragment of the medullary plate would be able to go on developing independently so far as to give rise to such a complex organ as the eye. The possibility suggested itself that the 'solitary eye' of such an egg may be connected with an

embryo which had sunken in the yolk-sac leaving the eye on the surface. The main objection to this would, of course, be that such an egg would die in a very short time, for the embryo could not possibly receive a sufficient oxygen supply; and the death of such a sunken embryo would soon cause autolysis of the ovum. More convincing proof seemed to be furnished by the fact that the yolk-sacs of the eggs, owing to the method of fixation, were translucent, while the embryo had turned white and opaque. If an embryo had sunken into the yolk-sac, it could thus easily have been detected. But, in spite of very careful examination of the ova with solitary eyes, not a trace of an embryo could be seen within their yolk-sacs. Moreover, in order to establish this fact of the independent development of the eye on the firm basis of unmistakable evidence, I sectioned one of these eggs. I have purposely chosen the egg in which besides the solitary eye several (some three or four) very small fragments of tissue could be observed on the yolk-sac, thinking that the latter ones might possibly offer a basis for the interpretation of the morphogenesis of the solitary eye.

The microscopic examination (fig. 22) of the sectioned egg proved that my interpretation of the case as that of a 'solitary eye' was perfectly correct. In the sections it can be plainly seen that the blastoderm had overgrown the entire yolk-sac just as this takes place in normal development. But no embryo can be seen in the yolk of any of the sections. On the yolk-sac besides the solitary eye there can be seen on some sections the fragments of tissue mentioned above, one of which makes the impression of a defective spinal cord and when followed out in successive sections is seen to give rise to the eye in question. Some blood vessels have also developed in a very abnormal fashion and no heart is present. Of the other amorphous tissue fragments one proved to be another eye, although very rudimentary in structure. The nervous elements of this second eye are obviously greatly inhibited in development, neither a choroid nor an iris are present, but the cornea and the lens have developed to a degree permitting of safe identification. The distance between the position on the yolk-sac of this eye

rudiment and that of the well developed solitary eye being as much as 262μ it seems evident that a blastolytic fragmentation of the early embryonic material and a subsequent shifting of the fragments to distant parts of the yolk-sac's surface has occurred.

Two more eggs with solitary eyes were cut into sections and a microscopic examination again confirmed the correctness of their being interpreted as such.

Several eggs were also found with asymmetrically monophthalmic and otherwise malformed embryos in which a completely isolated tissue fragment with a well developed eye could be seen on the yolk-sac at a distance from the embryo which made its connection with the same appear impossible. One of these eggs was sectioned and the microscopic examination revealed the fact that the isolated eye was in no connection whatsoever with the embryo.

In view of these findings no doubt can now be felt that the 'solitary eye' (embryone absente) and the 'isolated eye' (embryone praesente) offer ample evidence of the fact that a very small fragment of the medullary plate may be able to develop independently of the rest of the embryo's anlage far enough to give rise to such a complex organ as the eye. *This is, as far as I am aware, the first case on record of the independent development ('self-differentiation,' Roux) of the eye.*

4: Defects of the brain

The destructive influence of butyric acid and acetone on the developing egg of *Fundulus* manifests itself also in the severe injuries sustained by the central nervous system. In teratophthalmic embryos the brain was in most cases found to be abnormal to a greater or lesser degree. The forebrain may often be unpaired while the mid- and hind-brain of the same embryo are bilateral in symmetry. The hemispheres of one brain may often differ considerably in size and shape as well as in other respects. Thus, e.g., there may be seen a striking developmental inhibition in one hemisphere where most of the

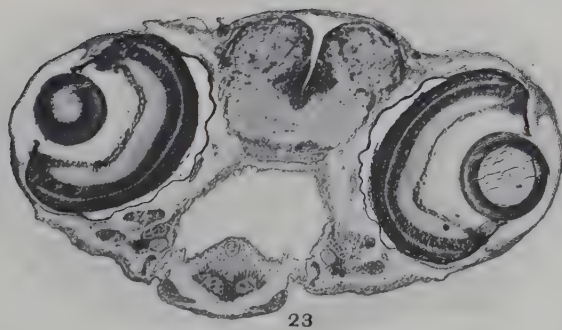
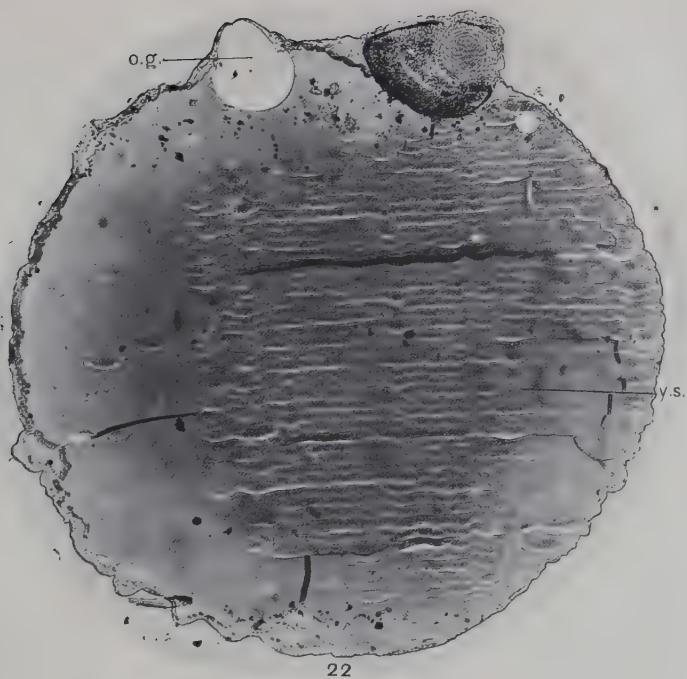


Fig. 22 Photomicrograph of section of egg with 'solitary eye,' (Cf. fig. 18); *y.s.*, yolk-sac, *o.g.*, oil globule space. $\times 80$.

Fig. 23 Photomicrograph of transverse section through the eye region of a normal *Fundulus* embryo, fourteen days old, one day after hatching. $\times 80$.

nervous elements had not proceeded beyond the neuroblast stage, while the other hemisphere may be made up of apparently well developed nerve cells and fibers. It was also often observed both in the brains and the spinal cords of teratophthalmic or otherwise defective embryos that wherever the neuroblasts failed to differentiate into nerve cells a great many large, clear and empty tissue spaces (figs. 26 and 27) were present. The probability suggests itself that these spaces in the living embryos may have been filled with body fluid. For, the heads of some defective embryos when observed in the living or even the preserved specimen were distended to a degree suggesting oedema. As was mentioned before, the same is true also for the ear vesicles. On microscopic examination it can invariably be seen that the usual size of the latter ones is due to (an apparently oedematous) distension of the semi-circular canals. A condition of hydrops is thus produced in the embryo which (since the fish brain has neither lateral ventricles nor a choroid plexus) might perhaps be considered as homologous with the internal hydrocephalus of man. Furthermore, the cranial (figs. 25 and 26) cavity may be unusually large, often containing some fibrin. Both this condition and the intracerebral oedema may often be present in the same embryo. Genetically these dropsical conditions probably are due to an arrest in the development of the blood or lymph vascular system.

5. Defects of the blood vascular system

There is a very wide range of variation in the deformities to which this system is subject. The heart is almost perfect in some embryos in which cyclopia is the only superficially noticeable defect. In more extremely malformed embryos, however, the heart may be only an exceedingly delicate, straight tube in some embryos, while it may be absent altogether in others. It is interesting to note in this connection that while acardia was frequently observed in eggs in which a whole although malformed embryo had developed, a heart, though usually more or less of a rudimentary structure, but functioning, could be

found in some eggs in which only meroplastic embryos or no embryo at all had developed.

While in some embryos the heart can be plainly seen to be connected with the great vessels of the embryo and indirectly with the larger vessels of the extraembryonic area, no such continuity exists in most of the deformed embryos which develop without a complete circulation, or, often without any circulation whatsoever. To J. Loeb ('93) belongs the credit for this remarkable discovery, which is now corroborated by Stockard's ('15) and my own findings. The blood vessels of the yolk-sac may sometimes be present in the form of irregular, dense, apparently continuous networks, or in some cyclopean embryos they may approach in pattern and size the normal blood vessels, while in cases of more extremely malformed embryos only blood islands may be seen scattered in the yolk-sac. Yet blood vessels are usually found in such cases in the embryo itself. It may well be said that only few embryos which develop in butyric acid and acetone solutions, while possessing blood vessels, have a circulation continuous with the extraembryonic area.

This accounts for the interesting fact that very often large lacunae filled with erythrocytes are seen in the bodies of some monstrous embryos as well as in the extraembryonic areas. These lacunae are very striking at the first glance at a living ovum on account of the bright red color of the erythrocytes. Another observation which was first recorded by Stockard ('15) and which I have also frequently made is that a large mesenchyme space, usually in the head region or sometimes in other parts of the body, may frequently contain many leucocytes of apparently the polymorphonuclear variety (fig. 24). The elements of the blood which come from different sources are thus seen to be isolated due to absence of a continuous system of circulation. The bearing of these data on the problems of vasculogenesis and haemogenesis is evident and I expect to discuss it elsewhere.

That these data may also have an important bearing on the genesis of some forms of hydrocephalus has already been pointed out above. It is easy to imagine that even in man a local in-



Fig. 24 Photomicrograph of a transverse section through the eye region of a monstrum synophthalmicum bilenticum (Cf. fig. 2); *l.c.*, leucocytes, *o.c.*, optic chiasma. $\times 100$.

hibition in the development of the blood and lymph vessels in the head region may result in accumulation of fluid in some parts of the head, even in the lateral ventricles of the brain due to lack of adequate drainage. Careful anatomical investigations of some well diagnosed cases of hydrocephalus may possibly bear out the validity of this assumption.

A case described by Smith and Birmingham ('89) may be of interest in this connection. They report a fetus aborted during the fifth month of pregnancy with general oedema due to complete absence of lymphatic vessels. On microscopic examination of the skin and subcutaneous tissue they found in the sections large spaces, "in some parts clear and empty, in others filled

with a colloid material, evidently coagulated lymph." From their appearance and position they concluded that they were dealing with greatly distended lymph spaces, the overdistension being the result of the absence of a lymphatic drainage system.

6. Deformities of the appendages

One of the most frequently found malformations concerns the fins. Both the pectoral and caudal are very often rudimentary (figs. 7, 9 and 10) and diminutive in size. In some deformed embryos the pectoral fins or all fins may be absent altogether (figs. 11, 14, 19 and 20) and the tail in such embryos is club-shaped. I have also often recorded embryos in which only one pectoral fin was present (fig. 8) while only one embryo was found with three pectoral fins. One is reminded by these deformities of the fish's appendages of well known cases in the human being with which they seem homologous. The club-foot in the human fetus and congenital absence of upper limbs in man have often been found. Likewise cases of supernumerary upper limbs have been recorded in man as well as in other mammals.

The fact that such defects can be produced in the fish by chemical action suggests that in mammals they may be due to like causes.

7. Duplicities

The tendency of butyric acid and acetone to produce twins seems to be only slight for I have observed only a few such cases. I have recorded only one case comparable to the 'Siamese twins' type of the human. In this egg two deformed embryos with a common heart had developed on opposite sides of the egg. Some other cases of twin formation found in these experiments belong to the type known as 'duplicitas anterior' (fig. 21) which Speeman ('04) produced experimentally by tying a ligature around the fissure between the first two blastomeres of the amphibian egg. Several cases of duplicity have also been recorded, the nature of which I expect to ascertain by microscopic examination.

THE MORPHOLOGY OF TERATOPHTHALMIA

After this general survey of the recorded monstrosities I shall now briefly consider the morphology of some such ophthalmic defects as I have so far been able to examine in sections with a view of a more exhaustive treatment of the topic in the complete account of the results of these investigations. Before, however, presenting a few of the cases which I have studied, some terms may be defined, the use of which to me seems to be desirable.

The various degrees of the one-eyed condition which have been recorded by previous writers (Speeman, Stockard, Lewis) as well as by myself, I shall henceforth classify in the following manner:

- I Monophtalmia asymmetrica (s. lateralis)
- II Cyclopia (s. Monophtalmia mediana) $\left\{ \begin{array}{l} \text{(a) perfecta} \\ \text{(b) synophtalmica} \end{array} \right.$
- III Synophtalmia $\left\{ \begin{array}{l} \text{(a) unilentica} \\ \text{(b) bilentica} \end{array} \right.$

The first term is well known because it already has been used by Ahlfeld and adopted by Stockard and so it will need no further comment.

In the case of cyclopia the distinction is made between 'perfect' ('true') cyclopia and 'synophtalmic' cyclopia. The first is to indicate the presence of a single median eye which on microscopic examination is found to be single throughout and nowhere exhibiting evidence of its being composite in character. Under the latter one will be classified such cases where on macroscopic examination a single median eye (with one lens) is found present, while the microscopic examination of sections reveals its composite character. Under 'Synophtalmia' will be classified cases of 'fused' eyes where the composite character of the eye (or eyes) is plainly discernible *in toto*. If such an optic apparatus should possess one lens only it will be designated as 'Synophtalmia unilentica,' while in the presence of two symmetrically placed lenses 'Synophtalmia bilentica' will be used as the descriptive term.

A few illustrative examples will now be given, after which a discussion of the morphogenetic factors of teratophthalmia will be taken up.

Figure 5 represents a case of unilentic synophthalmia. The egg was subjected between the second and third cleavages, —i.e., about $2\frac{1}{2}$ hours after insemination—to the action of 10 cc. of $\frac{1}{12}$ gram molecular solution of butyric acid for twenty hours and then transferred to pure sea-water. Already on superficial examination the composite structure of the eye is easily recognized. It is seen that the approximation of the two eye components is so close as almost to give the appearance of perfect cyclopia. Transverse sections (fig. 26, p. 549) show that the eye is composed of two incomplete optic cups facing each other and enclosing a single lens of about the usual size. The cornea and iris are normally developed and the retinal layer is well differentiated. Two optic nerves are seen to pass out of the eye in a few loose bundles of fibers and, after having formed a chiasma, to enter the opposite sides of the brain.

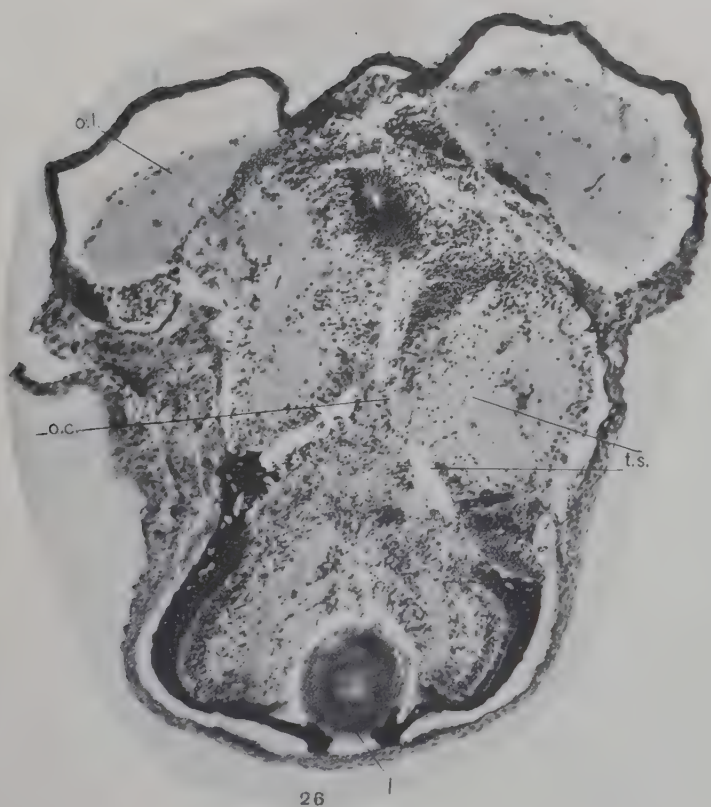
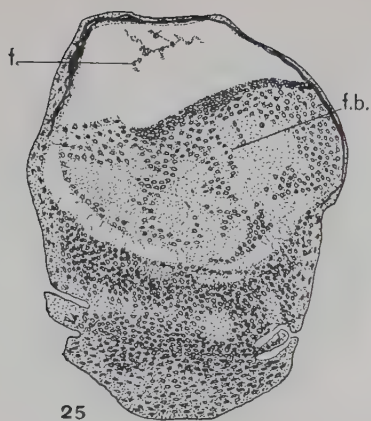
The incompleteness of the fused optic cups is probably due to the circumstance that at a very early stage of development a large part of the ophthalmoblastic material had been eliminated from development owing to the chemical alteration caused by the butyric acid. The injury sustained by the embryo must apparently have been the severest at the most anterior point of the main body axis, diminishing gradually posteriorwards. The following data seem to substantiate this interpretation. The forebrain is unpaired (fig. 25) and the rest of the brain is when followed in successive sections posteriorwards seen gradually to present more and more distinctly the condition of bilateral symmetry. The midbrain and hindbrain while being bilateral, exhibit, however, a certain other abnormality. The injury here was apparently mainly restricted to the blood and lymph vessels, the earliest anlagen of which seem to have been arrested in their development. This condition can be recognized by the great number of large, clear and empty spaces (fig. 26) in the tissues of the posterior parts of the brain, which in the living embryo have apparently been filled with fluid owing to

the existing imperfection in the circulation. A condition of oedema has thus apparently resulted from lack of drainage. No other abnormalities of these parts of the brain or any other part of the embryo can be seen, which makes it appear very probable that the anterior part of the embryo body is the most sensitive one and thus subject to the highest degree of injury.

In figure 2 is seen an eighteen days old embryo exhibiting the condition of 'synophthalmia bilentica.' This egg had been subjected to the action of 10 cc. of a $\frac{1}{16}$ gram molecular solution of butyric acid in 50 cc. of sea-water for twenty hours, after which time it was transferred to pure sea water. In the specimen *in toto*, the eyes, while being very close together, could not be considered as fused. On microscopic examination, however, it was found that the eyes were fused more posteriorly (fig. 24, p. 544) and that the fusion is the more intimate the more posterior is the section examined. If all sections be examined it can be clearly seen that the highest degree of the injury sustained by the egg due to the treatment is in the most anterior part of the embryo's body, i.e., in the region of the eyes. The abnormalities found in this part of the body besides the fused eye involve also the olfactory pits, which are so closely approximated as to be partially fused, and the forebrain, which is unusually small in size and unpaired. The transverse sections of this embryo are somewhat oblique and the double eye being somewhat asymmetrically located in relation to the chief body axis, in the figure the lens of one eye can be seen to be sectioned about midway while of the other lens the most posterior part is cut. The two lenses, however, can be clearly made out in the figure. The choroid coats which are imperfectly developed and the well differentiated

Fig. 25 Camera lucida drawing of a transverse section anterior to the eye region of a monstrum synophthalmicum unilenticum (Cf. fig. 5), showing unpaired forebrain, *f.b.*, greatly enlarged cranial cavity occupied by some fibrin, *f.* $\times 140$.

Fig. 26 Photomicrograph of a transverse section through the eye region of the same embryo as in figure 25, showing the two components of the synophthalmic eye, facing one another, with one lens, *l.* Many tissue spaces, *t.s.*, are seen in the brain. The cranial cavity in the region of the optic lobes, *o.l.*, is greatly distended, *o.c.*, optic chiasma. $\times 160$.



retinal layers are seen to be perfectly coalesced ventrally, while dorsally they arch inwards to leave an opening for the optic nerves. The latter come as separate bundles of fibers from each one of the eye components and fuse into one trunk just at the point of emerging from the double eye. This common optic nerve trunk is in other sections seen to enter only one hemisphere of the brain. The cavity between the sclera and the brain has widened out and is on both sides near the head integument occupied by large leucocytes of apparently the polymorphonuclear variety. These leucocytes are seen in all sections of the embryo densely filling spaces between the tissues or they may also be found more scattered in the mesenchyme. The blood vessels of this embryo as well as of its extraembryonic area are rather scarce, and the discontinuity of the latter ones being very striking, the suggestion is at hand that the circulation of the embryo was imperfect. This would account for the accumulation of white blood corpuscles in the mesenchyme as well as for the numerous apparently oedematous interstices which they often filled. Summarizing the abnormalities found in this embryo, it may well be said that the degree of injury sustained by it, being highest in the immediate region of the eyes, diminishes along the main body axis posteriorwards, the mid-brain and hindbrain, excepting the anomalies due to an inhibited circulation, being apparently normal in all other respects.

Of a much higher degree is the injury sustained by the case of perfect cyclopia with a supernumerary lens, cross sections of which are represented in figures 27 and 28. The egg had been subjected in the eight-cell stage to the action of 35 cc. of a gram molecular solution of acetone in 50 cc. of sea-water for forty-eight hours. The embryo when killed was twenty-seven days old. A single median eye is seen in a transverse section (fig. 27) which is smaller in size than a normal eye, the lens only being disproportionately large. All other structures of the eye, viz., cornea, iris, choroid coat and retina are present, the latter having differentiated in a defective manner. At a somewhat more posterior level of the brain, the following view is presented (fig. 28). Laterally from the eye on one side is seen a large well

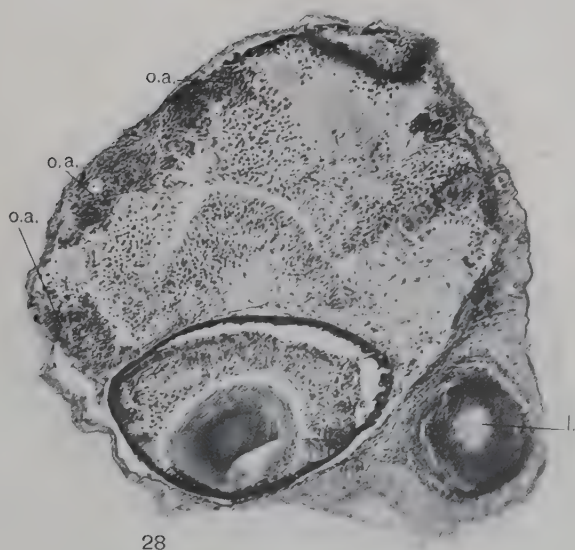


Fig. 27 Photomicrograph of a transverse section through the eye region of a twenty-seven days old cyclopean embryo, one day after hatching, showing a small median, imperfectly differentiated, eye with a disproportionately large lens. The forebrain is very abnormal, and tissue spaces, *t.s.*, point to oedema. From acetone solution (35 cc. gram molec. sol. to 50 cc. sea-water). $\times 160$.

Fig. 28 Photomicrograph of a transverse section of the same embryo as in figure 27, at a more posterior level, showing supernumerary lens, *l.*, on one side and optic anlagen on the other side of the cyclopean eye. $\times 160$.

differentiated lens surrounded by an epithelial capsule and anteriorly and laterally by a cornea, which is found to be in continuation with the cornea of the cyclopean eye. On the other side of the eye between its lateral border and the head integument is to be seen a large patch of cells with deeply stained nuclei and a little higher upwards on the same side (o. a.) and bordering the integument two more such patches of tissue can be seen in close approximation. On careful examination it was found that these three patches of cells represent fragmentary optic anlagen. The one of these optic anlagen which borders the eye has even differentiated into a small retinal layer which is in about the same stage of differentiation as the same structure of the cyclopean eye. There is only one optic nerve present which in more posterior sections can be seen to enter as a trunk one of the hemispheres. The brain is much deformed and more so anteriorly, where its symmetry is obscured, than posteriorly, where its bilateral symmetry can be recognized without difficulty. Many large clear tissue spaces can be seen in the brain in almost all sections which in the living apparently represented persistent early embryonic vascular anlagen and were filled with body fluid owing to lack of drainage caused by an imperfect circulation.

This embryo I regard as one instance of the perfect cyclopean condition, for only one complete eye has developed. Such indications as are present of the other optic anlage give us a clue to the genesis of the single-eyed condition in this case. Although the injury sustained by the embryo is not localized and is of a high degree, it is highest in the most anterior portion of the body, diminishing gradually posteriorwards along the main body axis. The anterior portion of the very early embryonic anlage has apparently undergone great destructive alterations of a blastolytic nature, owing to which the ophthalmoblastic material of one side was fragmented and dispersed while the corresponding material of the other side has been injured less severely and has given rise to an imperfectly developed median eye. The material which would in the normal embryo eventually be represented by the interocular area seems to have, owing

to some regulatory processes, moved lateralwards, where it has given rise to an independent lens. To the same regulatory process is it probably due that the ophthalmoblastic material of the less injured side has been shifted medianwards to give rise to the cyclopean eye.

The case of 'asymmetric monophthalmia' which I shall now describe will, I believe, also point to unmistakable evidence that in teratophthalmic embryos the sustained injury is usually the severest at the anterior end of the body.

The egg had been subjected for forty-eight hours to treatment with acetone, 35 cc. of a gram molecular solution of which were added to 50 cc. of sea-water. The embryo was killed one day after hatching when it was sixteen days old. On examination *in toto* there was seen to be present only one eye in the usual lateral position while the mouth occupied exactly the position of the missing eye. In transverse sections (fig. 29) it is seen that the one eye present is well developed and apparently normal in structure. No indication of another eye or optic anlage can



Fig. 29 Photomicrograph of a transverse section through the eye region of a monstrum monophthalmicum asymmetricum, from acetone solution (35 cc. gram molec. sol. to 50 cc. sea-water), sixteen days old, one day after hatching. The mouth, *m.*, occupies the position of the missing eye. $\times 120$.

be found anywhere in the sections and only one optic nerve is seen in the more posterior sections to pass out of the retina and terminate in the optic lobe of the opposite hemisphere. The brain is symmetric as far as its bilaterality is concerned, but is asymmetric in regard to the position occupied by the two hemispheres in relation to the main body axis. As can be seen in the figure, the hemisphere of the side where the eye has developed, is in its normal position while little can yet be seen of the other hemisphere, which has been shifted posteriorwards and comes to view in more posterior sections. The same posteriorward displacement has also affected the olfactory pit and the semi-circular canals of the side lacking the eye. There are no other abnormalities to be recorded for this embryo. The abnormalities found, however, justify the conclusion that the injury sustained by the early embryo was chiefly a unilateral one at the anterior end of the body. Owing to this injury the ophthalmoblastic material of one side has suffered complete destruction. On the same side, owing to subsequent processes of regulation, the mouth has arisen in what was to be the position of the eye and a posteriorward displacement of the brain hemisphere of the injured side has taken place. The sustained injury, while being lateral from the median axis of the body, was severest at its most anterior end where it has eliminated the material for an entire organ.

The cases described above and many more similar ones which have been studied led me to accept in the main the 'fusion theory' of cyclopia which has in recent years been advocated by Lewis ('09) and Speemann ('12) and to reject as untenable Huschke's ('32) view of the early single anlage of the eye which Stockard has quite recently ('13) adopted in his morphogenetic analysis of cyclopia.

Stockard, who was the first to produce experimental cyclopia in fish by chemical agents, has in his earlier work ('09) suggested that the developmental defect is due to the specific anaesthetic action of the chemicals (magnesium chloride, chloroform, ether, etc.) which he used. He thought that the giving off of the eye anlagen by the brain was inhibited often in an unequal manner

on both sides, thus giving rise by fusion of the inhibited anlagen to various transition stages between two normal eyes and cyclopia and anophthalmia. Recent investigations of McClendon ('12), however, who obtained similar results with a great variety of non-anesthetic substances, have caused Stockard ('13) to abandon his anesthetic theory of teratophthalmia. He now believes that the eye anlage in the medullary plate is single and median in position, that in normal development this single anlage eventually divides into two portions which move lateralwards, where they develop into the optic vesicles. If the embryo is subjected to the action of toxic chemicals this separation of the original single median optic anlage into two, may, he concludes, be inhibited to a greater or lesser degree and thus various degrees of the cyclopean defect may result. He even submitted the theory of the single optic anlage to an experimental test which, he believes, answered the query in the affirmative. It is unfortunate that Stockard's statements are not substantiated by better evidence than that which he brings forth, since he has failed to support his statements by illustrations of specimens *in toto* and in sections of the material which he regarded as permitting of such important conclusions. *Until this evidence is furnished, however, the theory of the single median optic anlage in the medullary plate would hardly seem to be acceptable.* On these grounds, we cannot agree with Stockard's conclusion on the morphogenesis of cyclopean defects.

The 'fusion theory' of cyclopia is, I believe, justified in the main, and has recently been ably supported by Speemann (l. c.), Mall (l. c.) and W. H. Lewis (l. c.). These authors assume a coalescence or fusion of two originally separate optic anlagen. Just how this fusion comes about may still be a matter of discussion. I think that Speemann's and Lewis' suggestions are very illuminating just on this point. Both these authors have produced all those conditions of one-eyedness which Stockard has obtained in his investigations, and which I have recorded in my experiments, a description of some of which is given above.

Both Speemann and Lewis have produced the teratophthalmic condition by mechanical injury of a small area at the ante-

rior end of the early embryo; and Lewis holds that the collapsing of the wound surfaces effected the approximation of the two optic anlagen. The degree of this approximation would depend upon the size of the fragment of interocular tissue which Speemann eliminated by constriction and Lewis by pricking. This, they conclude, would account for the various degrees of the cyclopean condition. Even asymmetric monophthalmia can in this way be accounted for, as it is easy to imagine that in the experiment the injury inflicted to the embryo may sometimes be somewhat lateral from the embryo's main body axis and that a complete eye anlage may thus be destroyed. The teratophthalmic condition would then, as Speemann points out, have to be regarded as a 'defect' (evidently meaning a mechanical defect) rather than a developmental inhibition.

My own conclusions are very similar to those arrived at by Speemann and by Lewis. I have, however, found it necessary to modify the fusion theory of cyclopia to conform to Stockard's and my own findings. The explanation offered by these authors is open to the criticism made by Stockard, namely, that "cyclopean eyes are rarely in size and extent equal to the sum of the two normal eyes combined." It is obvious that this objection is justified and that conclusions based on results obtained from mechanical experiments cannot be extended to cover the results of the chemical experiment or to account fully for the occurrence of the cyclopean defect in nature under unfavorable environmental conditions.

The following modification of the coalescence theory of cyclopia meets the objection raised by Stockard, covers the results of the chemical experiment and thus, I believe, may be extended to the morphogenesis of various cyclopean defects in nature, where the causal factor is undoubtedly a chemical one.

When the fertilized egg is subjected to the action of toxic substances it will sustain an injury, which—depending upon the stage of development, the substance used and the strength of its solution—may be a general one, i.e., involving the whole or a large part of the embryo's body, or a locally restricted one. The results of Stockard's and McClellendon's work, as well as some

results of my own experiments, point to a blastolytic injury of a restricted area at the anterior end of the early embryo's body in the case of teratophthalmia. Child's³ ('09, '12) important discovery of the 'axial gradients', according to which the anterior end of a flat-worm's body is the most sensitive one to the action of injurious substances would seem well to justify this assumption. In the early vertebrate embryo, before the organs have been differentiated, probably very similar physiological conditions obtain, and thus we may well assume that its anterior end is the point of least resistance. When the egg is acted upon by a toxic substance, a restricted area at the anterior end of the embryo's median body axis becomes so altered chemically as to be eliminated from further development or it may go on developing to a certain point beyond which it is chemically unable to proceed. This restricted area at the anterior end of the body axis is the region between the future optic anlagen or even the region of those anlagen. The size of the injured area at the anterior end is probably subject to considerable variation, and thus it may comprise the material which would normally correspond to the future interocular area and cause an approximation of the potential optic anlagen or it may extend even over the latter ones, thus eliminating parts of them, while the uninjured parts would coalesce after approximation and form any one of the various degrees of the synophthalmic condition. Or, finally, the injured area may comprise the whole of one potential optic anlage and little or no material of the future interocular area, thus causing the embryo to develop into a cyclopean monster if the uninjured optic anlage is shifted medianwards, or into an asymmetrically monophthalmic monster, if no such change in the position of the uninjured or less injured ophthalmoblastic material takes place.

³ Child offers an interesting interpretation for this high degree of sensitivity. According to him the rate of the metabolic reactions seems to be the highest at the anterior end of the planarian's body, decreasing gradually along the main body axis in the direction away from the head. This theoretical postulate of the metabolic 'axial gradient' was substantiated by the rate at which various points along the body axis have given off CO₂, the measurements having been made by Tashiro with his own biometer-method.

Here too, the size of the chemically injured area may vary and thus in some instances a small fragment of the injured potential anlage may survive and develop into a diminutive whole, but somewhat rudimentary, eye, or into an eye fragment with a well differentiated retinal layer and choroid coat.

However, it is necessary to assume that the injury which results in teratophthalmia is sustained at a very early stage of development. At that time the volume of the area which receives the injury is relatively small and such minute parts of the embryo as may represent the potential double anlagen of the eyes, are, since growth proceeds in a cubic proportion, relatively much nearer each other than they would be at a somewhat later stage, e.g., in the embryonic shield. This would account for the fact that the cyclopean eye may be very small in size, much smaller even than the normal eye. For, at this stage, the eliminated area may contain much more material than of one potential eye. The remaining ophthalmoblastic material may undergo some regulatory process to form eventually a single eye of corresponding size or a double, fused eye if enough of the ophthalmoblastic material of both sides survives, or finally if the injury sustained by that material be so extensive as to comprise all of it, the condition of anophthalmia may be the result. This conception of the morphogenesis of teratophthalmia, while recognizing the coalescence theory of cyclopia as justified, also meets the objection which Stockard raised to Speemann's and Lewis' generalizations, namely, that the cyclopean eye is often much smaller than the sum of two normal eyes combined. At the same time, it makes it appear unnecessary to resort to a theory whose probability is so questionable as that of the "single median optic anlage in the medullary plate" (Stockard).

* * *

The mechanism involved in the action of butyric acid and acetone in bringing about the great variety of recorded effects will have to be taken up as one of the further steps of this investigation. At the present time, I can only state that there seems to occur in the eggs when subjected to the action of these solutions

an elimination of material of the blastomeres or of the germ-disc and probably also of the yolk-sac. This elimination of material may be due either to the precipitating or solvent effect respectively of the chemicals which were used in these experiments. Since many eggs were found with living but extremely malformed embryos, the yolk-sacs of which were ruptured allowing some yolk to escape, the suggestion is at hand that another factor—some force like a temporarily increased internal osmotic pressure—may by its action have brought about the fragmentation of the germ-substance. On examining many eggs in which only amorphous tissue fragments can be found and the eggs with 'solitary eyes' (embryone absente) or eggs with 'isolated eyes' (embryone praesente) one gains the impression that either the blastomeres or the germ-disc had been blastolytically fragmented owing probably to both physical and chemical factors. These tissue fragments sometimes appear at such great distances from each other, or even from a malformed embryo, that there seems to be no doubt left that they have moved out of their original position along the axis of the embryo. Having examined many thousands of these pathological ova I believe that I possess enough evidence to justify the assumption of blastolytic processes of a physical or chemical nature, such as fragmentation due to a temporarily increased osmotic pressure or to chemical alteration of some parts due to the solvent or precipitating effect respectively of the chemicals used in these experiments. Mall speaks (l. c.) of a similar process which he assumes for some pathological human ova, and which he terms 'dissociation of cells.' The effects of these apparently blastolytic processes vary enormously. For whatever parts survive them, may go on developing into a whole defective, or a meroplastic, embryo, or even into an isolated organ.

Just what brings about this great range of variation in the noted effects can at present hardly be more than conjectured. It would seem probable that the stage in which the egg is subjected to the action of the toxic solution may play an important part in that respect. For as Conklin ('12) has shown ". . . stages during kinesis are more susceptible to modification than stages

during interkinesis. Almost all persistent alterations of structure occur during cell division, few of those which occur during the resting period are permanent." However, this and similar other inquiries must be left to future investigation.

CONCLUSIONS AND SUMMARY

1. Starting from the assumption that monstrous development is due to parental metabolic toxemia, experiments were performed in which *Fundulus* eggs were subjected to the action of some substances occurring in the blood or urine respectively of man during metabolic disturbances.

2. With two of these substances, i.e., butyric acid and acetone, positive results have been obtained, a great variety of monsters having been produced which are analogous or homologous respectively to human and other mammalian monsters. The monstrosities concern the eyes (cyclopia, synophthalmia, monophthalmia asymmetrica and anophthalmia), the ear vesicles, the olfactory pits, the mouth, the central nervous system, the heart and blood vessels, the fins (unpaired fin, absence of pectoral fins or all fins, club-tail, etc.) and body form.

3. A condition of hydrops was found in many embryos, due apparently to blood vascular abnormalities which might be considered as homologous to some forms of hydrocephalus in man.

4. In many eggs parts of the embryonic material have suffered destruction, while the remaining parts have developed into anterior hemiembryos or other meroplastic embryos.

5. Eggs have been found in which one eye has developed from a small fragment of the medullary plate independently of an embryo (the 'solitary eye,' the 'isolated eye').

6. Regarding the mechanism of action of butyric acid and acetone the conclusion has been reached and some evidence offered that the various monstrosities are brought about by a process of blastolytic fragmentation due to some factors not yet ascertained.

7. Regarding the formation of the various degrees of the 'cyclopean' defect it is concluded that the fusion theory of Speeman

and Lewis is justified in the main. An additional assumption is made, namely, that the blastolytic process which eliminates parts of the potential interocular or ophthalmoblastic material takes place at a very early stage of development (i.e., before the formation of the embryonic shield).

8. The results obtained tend to justify the assumption that monstrous development may be due to metabolic toxaemia.

The experimental part of this work has been carried out at the Marine Biological Laboratory at Woods Hole, Mass., during the summer of 1914. It is a pleasure to me to acknowledge my indebtedness to the director, Dr. F. R. Lillie, for the facilities granted. I am also under great obligation to Professors Conklin and McClure and to Dr. E. N. Harvey, whom I have often taken occasion to consult on some points of the work. For many courtesies I am indebted to Professor Dahlgren and Mr. W. E. Hoy.

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THE DEVELOPMENT OF THE LYMPHATIC SYSTEM IN THE LIGHT OF THE MORE RECENT INVESTI- GATIONS IN THE FIELD OF VASCULOGENESIS

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Does the endothelium of the lymphatic system arise, at any time or place, in a discontinuous manner and independently of that of the veins? As we shall see, the determination of this question constitutes a solution of the lymphatic problem.

The view that lymphatic endothelium spreads continuously and uninterruptedly throughout the body of the embryo from the endothelium of the veins, is merely an extension, and application to the endothelium of the lymphatic system, of the well-known view held by His, that the endothelium of the intra-embryonic haemal vessels grows continuously and uninterruptedly into the embryo from the yolk-sac angioblast. Such a method of origin necessarily implies that all intra-embryonic endothelium arises only from a pre-existing endothelium which takes its origin in the yolk-sac, and that in the body of the embryo a discontinuity of origin never occurs.

The view opposed to the 'ingrowth' or 'angioblast' theory of His has been closely associated with the names of Rückert and Mollier (1). This view consists in the claim that the endothelium of the intra-embryonic haemal vessels develops *in situ* in the body of the embryo, and that it is not derived from the yolk-sac angioblast.

Since the lymphatics merely represent a component part of a general vascular system, to which the haemal vessels also belong, the probability at least, is that, in the genesis of their endothelium, and in the establishment of a continuous system of vessels, the lymphatic and haemal vessels should follow a common genetic

plan. Let us consider, in the light of the more recent investigations in the field of the vascular system, what this plan may be.

It is not the purpose of the present paper to give a review of the investigations of those who have consistently maintained a local origin for the endothelium of the intra-embryonic haemal vessels. It is only necessary to refer to the more recent and excellent paper by Schulte in which such a review and critical analysis of their work is given.

The investigations of Schulte (2) on the mammalian embryo have shown in particular, that the yolk-sac angioblast cannot possibly aid in forming the endothelium of the umbilical veins; Schulte has also demonstrated in a most convincing manner, that the endothelium of other main intra-embryonic haemal vessels develops *in situ* from mesenchymal cells.

It should be clearly borne in mind that, until quite recently, the investigations which have dealt with the origin of intra-embryonic endothelium have not been experimental in character, but have been based largely upon a study of fixed material in which, however, a local and discontinuous origin of blood-vascular anlagen has been observed.

Let us now see how the view that the endothelium of the intra-embryonic blood-vascular system develops *in situ*, and does not grow into the embryo from the yolk-sac, has been borne out by experiment.

Two types of experiment have thus far been made to determine this question: (1) The partial separation of the embryo from the yolk-sac, or, the complete separation and isolation of a portion of the embryo from the rest of the embryo and from the yolk-sac, at a time prior to the possible invasion of the embryonic axis by the yolk-sac angioblast; (2) by observing the effects produced on the developing blood-vascular system in embryos which have been allowed to develop under the influence of anesthetics or other chemical agents.

The experimental investigations of Hahn (3), and Miller and McWhorter (4) have shown, by effecting a separation on one side between the body of the chick embryo and the yolk-sac, before vessels have appeared in the area pellucida, that blood

vessels make their appearance in the body of the embryo in a typical manner on the operated side. These vessels differ from those on the unoperated side only in size and rate of development, differences which may be correlated with their reduced drainage area and the consequent diminished quantity of circulatory fluid.

These experiments of Hahn, and Miller and McWhorter have conclusively shown that the yolk-sac angioblast cannot have grown into the embryo on the operated side. In order to eliminate the possibility, however, that the vessels on the operated side may not have been formed *in situ*, but by an invasion of angioblast from the normal unoperated side, Reagan (5) has recently completed a set of experiments in my laboratory which conclusively disprove this contention. Instead of separating only one side of the embryo from the yolk-sac, Reagan has been able to develop the heads of chick embryos, which had been completely separated from the rest of the embryo and from the yolk-sac, and in which endothelial lined vascular channels of mesenchymal origin invariably appear. As in the case of the experiments of Miller and McWhorter, the operations were performed at a time before it would have been possible for the intra-embryonic tissue to have been invaded by yolk-sac angioblast.

Gräper (6), under the direction of C. Rabl, performed a set of experiments on chick embryos, somewhat similar to those of Hahn, and Miller and McWhorter, and, although he noted the presence of independent blood-islands in the body of the embryo, he was unable to interpret them as having been formed *in situ*.

Jacques Loeb (7) was the first to observe the effects produced by certain chemicals (NaCN) on the developing blood vessels in fish embryos. He was able to produce a condition in which a beating heart and blood were present, but no circulation; a condition which, as stated by Schulte, can hardly be reconciled with the doctrine that the vessels of the embryo have a primitive continuity of lumen with those of the yolk-sac, for it is inconceivable that in such circumstances, a beating heart could fail to effect a circulation.

The investigations of Stockard (8) supplement and coincide with those of Hahn, Miller and McWhorter, Reagan, and Loeb in a most decisive manner. Stockard has shown that, not only do anesthetics arrest the development of the intra-embryonic blood vessels in the embryos of *Fundulus*, at an early ontogenetic stage, but in such a manner that no doubt can now exist that, under normal conditions, these vessels are formed *in situ* by a concrescence of independent and discontinuous anlagen, and that their endothelium is derived directly from mesenchymal cells. It is interesting to note in this connection that Wenckebach (9) had already observed in the body and yolk-sac of the living fish embryo (*Belone longirostris*), that mesenchymal cells play an important rôle in the formation of vessels and sprouts. In their general features the observations of Wenckebach have been confirmed by Raffaele (10).

It is thus seen that experimentation bears out the observations made upon fixed and living material, that the intra-embryonic blood-vascular channels do not grow into the embryo from the yolk-sac, but are formed *in situ* by a concrescence of independent and discontinuous anlagen, whose endothelium is formed from intra-embryonic mesenchymal cells.

The vascular plexus formed in the extra-embryonic area of the vertebrate embryo, is as we know, at first represented by discontinuous, independent and circumscribed anlagen, the cells of which possess a local origin. Clefts or spaces, the future lumina of the plexus, soon make their appearance in a discontinuous manner amongst the cells of these anlagen, and it is by a concrescence of these vascular spaces that a continuous system of vascular lumina is finally formed. The cells which constitute the walls of these vascular spaces become transformed into the endothelium and, when blood-islands are present, the more centrally situated cells form the primary blood cells. It is interesting to note in this connection that McWhorter and Whipple (11) have recently been able to demonstrate and record photographically the concrescence of separate vascular anlagen in the area pellucida of the chick's blastoderm *in vitro*.

If we compare the development of the intra-embryonic blood-vascular channels, as determined by observation and experiment, with that of the plexus which arises on the yolk-sac, we find, in the genesis of their endothelium from mesenchyme, and in their formation by a concrescence of independent anlagen, that the intra- and extra-embryonic blood-vascular channels follow exactly the same genetic plan.

If one attempted to follow the development of these intra- or extra-embryonic blood-vascular channels by means of injections, it is evident that this method would reveal only the extent to which a continuous system of injectible lumina had been established at the time the injections were made. It would fail completely to reveal the facts which have been definitely determined by experiment, that the injectible lumina had been previously formed by a concrescence of independent and uninjectible vascular spaces, and that the endothelium which forms the walls of these lumina had been formed *in situ*, not from a pre-existing endothelium, but from mesenchymal cells.

Since we now know that the intra-embryonic blood vessels, like those in the yolk-sac, are formed by a concrescence of independent anlagen, and that their endothelium is formed *in situ* from mesenchymal cells, the question naturally confronts us as to the method by means of which these independent anlagen become connected with one another to form a system of vessels with continuous lumina, that extend throughout the body of the embryo.

There appear to be only three possible methods by means of which such connections could take place: (1) Either by means of a proliferation or migration of the cells of which the original independent anlagen are composed; (2) by a further local *in situ* differentiation into endothelium of the embryonic cells which intervene between the independent anlagen; or (3) by a combination of these two methods.

We all recognize the fact the endothelium, like other tissues of the body, is capable of growth after it has once been formed. In no other manner could we account for the increase in size

which blood vessels undergo in the embryo after they have attained their adult structure and form. It is also possible for anastomoses to be formed between different blood vessels by means of a growth or sprouting of their endothelial walls, so that, in some cases, an increase in their extent, through growth, may actually take place. It is therefore quite probable that growth may play a considerable rôle in establishing a conrescence between the independent endothelial-lined anlagen of the blood-vascular system. From whatever standpoint it may be considered, however, the growth of an endothelium is a feature of secondary significance as regards the problem at hand, since the main question at issue does not concern the possibility that endothelium may or may not grow, but rather how the endothelium is formed that does the growing.

The distinction between the actual genesis of endothelium and the growth it may undergo after it has once been formed is naturally one that has been disregarded by those who maintain that intra-embryonic vascular endothelium is not directly a product of mesenchymal cells. A special specificity has therefore been attributed by the supporters of the 'angioblast' theory to the endothelium of the intra-embryonic vascular system, on the ground that it takes its origin only from the yolk-sac angioblast. In accordance with this view, it is by means of one continuous and uninterrupted growth of a pre-existing endothelium (yolk-sac angioblast) throughout the body of the embryo, that the endothelium of the blood-vascular and lymphatic systems is formed.

Since the 'angioblast' theory of His no longer holds, the question of the specificity of tissues is involved in the vascular problem only to the same extent as is the case for any other tissue in the body. Whether the mesenchymal cells of the embryo are in an embryonic or undifferentiated state, and capable of further differentiation into cells which form muscle, connective tissue, endothelium, etc., is entirely beside the question; provided we know that the product of these intra-embryonic mesenchymal cells actually forms endothelium and that the latter is not derived from the yolk-sac angioblast. Also, the question con-

cerning the origin of these mesenchymal cells, whether derived from entoderm, mesoderm or mesothelium, does not concern us here. The main point at issue is the establishment of the fact that the endothelium of the intra-embryonic haemal vessels is the product of a local *in situ* differentiation of certain cells in the embryo which have not been derived from the yolk-sac angioblast.

Let us now compare these conditions of the intra-embryonic blood-vascular system, as determined by sections and experiment, with those of those of the embryonic lymphatic system.

Our knowledge of the embryonic lymphatic system is gradually approaching a state where, in such forms as teleosts and amphibia, it may also be possible to determine by experiment how the lymphatic system is formed. A thorough knowledge of the lymphatic channels and the order of their appearance in the normal embryo would be quite essential, however, before experiment could be successfully applied. Since the anlagen of the lymphatics do not make their appearance in the embryo under normal conditions until after the veins have been established and have begun to function, it is quite possible, in cases of arrested development of the venous system, as demonstrated by Stockard in *Fundulus*, that development might never be successfully carried to the lymphatic stage. Be this as it may, until the problem has been tested by experiment, our knowledge and interpretation of lymphatic development must, for the present, be based upon the observation of fixed and of living material, and its comparison with the known developmental stages of the blood-vascular system, as observed in fixed and in living material, and as verified by experimental means. If it can be shown that the anlagen of the lymphatic system present exactly the same conditions in fixed and in living material, as those of the blood-vascular system, it is reasonable to infer that in their development the lymphatic and blood-vascular systems follow exactly the same genetic plan. *If one were to observe that in certain cases intra-embryonic blood vessels were formed in the living embryo by a sprouting or growth of a pre-existing endothelium, would he now be justified in claiming that all of the remaining*

blood vessels of the embryo were formed in the same manner? In view of the fact that we now know that intra-embryonic blood vessels are not all formed in this manner, it would seem that a similar interpretation might also apply to the lymphatics.

Whatever else the case may be, in view of the above-mentioned experimental investigations of Hahn, Miller and McWhorter, Reagan, and Stockard, it can now be definitely stated that the endothelium of the lymphatic system is neither directly nor indirectly a product of the yolk-sac angioblast. Such being the case, it must either arise *in situ*, like the endothelium of the intra-embryonic veins, from cells other than from a pre-existing endothelium; or, be a product entirely of the endothelium of the veins. If the former case be true, the endothelium of the lymphatic system should present exactly the same independent and discontinuous method of origin in the embryo as that of the extra- and intra-embryonic haemal vessels; and, if the development of the lymphatics were followed by the injection method, the same restrictions as regards the injectibility of its independent anlagen should also necessarily apply. On the other hand, if the lymphatic system is entirely a product of the endothelium of the veins, its origin from mesenchyme should naturally never occur. *As a matter of fact, since intra-embryonic vascular endothelium has been shown by experiment to be a local product of mesenchyme, there now remains no valid reason or significance in the claim, as regards its specificity, that lymphatic endothelium is solely a product of that of the veins.*

Let us examine the evidence at hand and see whether the endothelium of the lymphatics, like that of the haemal vessels, develops *in situ* in the mesenchyme, or whether it forms an exception to that of the haemal vessels, and sprouts continuously and uninterruptedly throughout the body of the embryo from an endothelium already formed.

It is not the purpose of the present discussion to give an historical review of the literature bearing upon the development of the lymphatic system but merely, on the basis of comparison, to call attention to the evidence in favor of the view that the lymphatics, like the haemal vessels, are formed by a coneres-

cence of independent and discontinuous anlagen, and that their endothelium arises *in situ* from intra-embryonic mesenchymal cells.

A principal contention of Huntington and McClure (12) regarding the development of the lymphatic system has been that its anlagen arise independently and discontinuously in the embryo, and that its endothelium does not spread continuously and uninterruptedly throughout the body from the endothelium of the veins. We have repeatedly shown that the lumina of the lymphatics are formed by a concrescence of discontinuous and independent lymph vesicles or lymph spaces, and that the cells which constitute the walls of these spaces are derived *in situ* from mesenchyme and not from the endothelium of the veins. In the early stages of our investigations we laid especial stress upon a plan of development for the lymphatic system of mammals which we described under the name of the 'extraintimal' theory of lymphatic development, and which may be briefly described as follows: The development of the thoracic ducts (13) and mesenteric (14) lymphatics in the cat is correlated with the degeneration of certain venous channels, many of which are tributaries of the azygos division of the supracardinal veins (15). A series of independent lymph spaces arise discontinuously in the mesenchyme external to the intimal lining of these degenerating vessels and, as these lymph spaces gradually become concrescent to form continuous channels, the latter, following a line of least resistance, utilize the static line vacated by these degenerating veins. In this manner certain of the main lymph channels of the mammalian embryo follow the course of and finally occupy completely the territory formerly occupied by veins. This principle of extraintimal replacement of abandoned venous channels by lymphatics accounts for the sinistral drainage plan finally assumed by the thoracic duct system in the embryo of the cat. The cranial or azygos division of the left thoracic duct of the embryo persists as the main line of drainage in the adult, in correlation with a degeneration in the embryo of the left supracardinal (left azygos) and left postcardinal veins and the left duct of Cuvier.

It is evident and appears clearly in our earlier publications, that the fundamental plan of development followed by these replacing lymph channels does not depart from that followed by other channels, either in mammals or in any other vertebrates where the development of the lymphatics is unaccompanied by the replacement of degenerating veins. Where, as in the case of the trout, lymph channels do not develop along the course of degenerating veins, an extraintimal replacement of a degenerating vein by a lymphatic necessarily does not occur. *It is therefore plain that the extraintimal replacement, as described by us, possesses only a mechanical significance, and is merely an adaptation of a common plan of lymphatic genesis, through the concrescence of independent anlagen, to the local conditions which prevail only in certain districts of the mammalian embryo.*

The same general plan of development as outlined above by Huntington and McClure for the lymphatic system of the cat has also been found by Kampmeier (16) to occur in the embryo of the pig. His description of the independent and discontinuous anlagen of the thoracic ducts which he found in the injected pig embryo loaned him by Professor Sabin, needs no further comment.

F. T. Lewis (17) has described the presence of a chain of discontinuous 'lymphatic spaces' (endothelial-lined anlagen) in the rabbit embryo which lie along the azygos veins in the path of the future thoracic duct. He regards these anlagen, however, as having been detached from the veins. Concerning these multiple anlagen of Lewis, Sabin (18) has stated as follows:

Since these spaces are lined with a definite endothelium, they form a much more serious obstacle to the theory of growth of the lymphatics from the endothelium of the veins than the more indefinite spaces to be found in earlier embryos, and I cannot but think that if these multiple endothelial-lined isolated spaces do exist along the veins in later stages, they would form serious evidence against the theory of the origin of the lymphatics from the veins. Or at least if the lymphatics, in their growth, do pick up isolated endothelial-lined spaces, we shall again be left without a clue as to the origin of the lymphatic system.

It is significant to note that, although Sabin considers these isolated endothelial-lined anlagen of Lewis as having been

detached from the veins, she nevertheless now recognizes their existence in the pig embryo, and regards them as entering into the formation of the thoracic duct (19, 1911, p. 424).

The point I wish to emphasize in this connection is that Sabin now recognizes the fact that lymphatics may be formed by the concrescence of multiple and independent endothelial-lined anlagen and that she has thus far presented no valid evidence that these anlagen have been detached from the veins.

Sala (20) and more recently Miller (21) have shown that the thoracic ducts of the common fowl are formed by a concrescence of independent and discontinuous lymph spaces and that their endothelium is formed *in situ* from cells other than those which constitute the endothelium of the veins. Miller has further made the important discovery that groups of blood cells develop in the mesenchyme along the line of the thoracic ducts and that the latter subsequently convey these blood cells to the venous circulation. We therefore find that hematopoiesis may actually occur in connection with the development of certain lymph channels, a condition which Huntington (22) has also recently verified for certain lymphatics of mammals.

West (23), by a study of injected and uninjected embryos, has recently found that the posterior lymph heart of the common fowl develops in the mesenchyme and secondarily establishes a connection with the veins. He has also found that hematopoiesis occurs in the mesenchyme in relation to the independent anlagen of the lymph heart, and states that the blood cells thus formed are not to be confounded with those which may later back into the lymph heart from the veins (see E. L. Clark, Anat. Rec., vol. 6).

Huntington (24), in a paper on the development of the lymphatic system in reptiles (chelonians, lacertilia), has shown that the systemic lymphatics develop in the mesenchyme independently of the endothelium of the veins. A particular feature of his investigation is that he was able to demonstrate that the periaortic lymph channel in *Chelydra serpentina* arises in the mesenchyme in an area entirely free of veins.

Stromsten's (25) investigations on the development of the lymphatic system in reptiles (chelonians) have led him to conclude that the lymphatics are formed by a concrescence of independent and discontinuous lymph spaces and that lymphatic endothelium is formed *in situ* from mesenchymal cells. His observations were based largely upon a study of injected embryos, and showed that the injecta did not reach the independent anlagen of the lymphatics, prior to their concrescence with one another to form a system of continuous lumina which had established a communication with the veins.

Fedorowicz (26) and more recently Kampmeier (27), have shown that the continuous lumina of certain lymphatics are formed in the amphibia (anura) by the concrescence of originally independent and discontinuous lumina. They conclude, however, that the endothelial walls of these lumina have been derived from the endothelium of the veins. E. R. Clark (28) regards the lumina of the developing lymphatics in amphibia (in tail of larval amphibia) as always continuous and capable of injection, while Fedorowicz and Kampmeier describe them as discontinuous at the start.

The writer (29) has demonstrated the presence of discontinuous and independent lymph vesicles in the trout embryo, which cannot be injected from other lymphatic anlagen or from the veins. Many of these vesicles arise in the mesenchyme remote from the veins, and no connection can be observed between their endothelium and that of the veins or that of any other lymphatic anlagen. One of these independent lymph vesicles, the subocular lymph sac, can actually be observed in the living trout embryo. On account of the relatively large size of this vesicle it has proved a most favorable object for experimentation and for study in sections, not only in proof of the fact that it arises independently of the veins, but also that its endothelium is of mesenchymal origin.

Allen (30) has investigated the development of the lymphatic system in *Polistotrema* (*Bdellostoma*) *stouti* and speaks of the lymphatics of fishes as veno-lymphatics. He states: "I expect to show that the main factor in the construction of the veno-

lymphatic system is the same as was described for the caudal lymph hearts, namely, the formation and union of certain mesenchymal spaces."

Allen, independently of Miller, has also observed that an active hematopoiesis occurs in the mesenchyme in relation to the developing caudal lymph hearts of *Polistotrema*.

Except for differences of opinion regarding the origin of lymphatic endothelium, it may be observed that the above-mentioned investigators agree for the most part that the continuous lumina of the lymphatics, like those of the haemal vessels, are formed by a concrescence of independent and discontinuous anlagen.

If we disregard entirely the personal equation which may have influenced any or all of the above-mentioned investigators to interpret their findings in accordance with one or the other view, the fact still remains that the anlagen of the lymphatic system, as observed in sections of injected and uninjected embryos, have been found to be identical with those of the intra-embryonic blood-vascular system, which has been shown by sections and experiment to be formed by a concrescence of independent anlagen, and its endothelium to be formed *in situ* from mesenchymal cells. *Since we possess exactly the same kind of evidence in favor of the mesenchymal origin of lymphatic endothelium, as we formerly did for that of the intra-embryonic haemal channels, before experiment was applied, it therefore seems highly improbable that the endothelium of two sets of similarly appearing anlagen, belonging to the same general organ system and developing side by side, should differ in its mode of origin, rather than follow a common genetic plan.*

We know that the lymphatics, both in the embryo and in the adult, establish a permanent communication with the veins at typical points (31). The question therefore arises, what rôle, if any, may be played by the veins in establishing such communications with the independently formed lymphatics? In the development of the general vascular system which includes the arteries, veins and lymphatics, the end result desired is the formation of a connected system of vessels which subserve definite functions in the economy of the general vascular system.

If the general vascular system develops progressively in a uniform manner, by a concrescence of independently formed anlagen, and the lymphatics, as is the case, form the last link in completing the chain, it is evident that the same factors should account for the establishment of a connection between the veins and the independently formed lymphatics as between the independently formed anlagen of which the veins and lymphatics are originally composed. Such a connection could alone be established, either by a growth or sprouting of the endothelium of the veins; by means of a further *in situ* differentiation into endothelium of the mesenchymal cells which intervene between veins and the independent anlagen of the lymphatics; or, both of these factors might be involved. If a connection should be established by a sprouting of the endothelium of the veins, such sprouts would possess no significance beyond the fact which we all recognize, that all vascular endothelium is capable of growth after it has once been formed. The question, however, is not whether endothelium is capable of growth, but rather what are its limitations and how is the endothelium formed that does the growing. It is therefore evident, if, at the points at which the lymphatics establish permanent communications with the veins, venous endothelium should contribute to the formation of the lymphatics, it would play only a subsidiary rôle, and serve only as a means, in common with the endothelium of other independently formed vascular anlagen, of bringing two independently formed portions of the vascular system into communication with each other to form a continuous system of channels. Such veno-lymphatic connections have been hitherto described by Huntington and McClure (32) under the name of 'venolymphatics.' It is evident, however, that these 'venolymphatics' would not differ, in any sense, from other connections, where a similar growth of endothelium is concerned, when made for the purpose of establishing a connection between any of the other independently formed anlagen of the general vascular system.

To sum up: The development of the general vascular system—haemal and lymphatic vessels—is a uniform process, which consists in a local origin (genesis) of endothelium from mesenchy-

mal cells and a growth of endothelium after it has once been formed.

In view of what has been said above, it would therefore appear that the lymphatic problem, in its broadest sense, should not be interpreted in terms either of a venous or non-venous origin, but rather in terms of the uniform phases of genesis and growth which may characterize the establishment of vascular channels in general.

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BOOKS RECEIVED

The receipt of publications that may be sent to any of the five biological journals published by The Wistar Institute will be acknowledged under this heading. Short reviews of books that are of special interest to a large number of biologists will be published in this journal from time to time.

THE INVESTIGATION OF MIND IN ANIMALS, E. M. Smith, Moral Sciences Tripos, Cambridge, 194 pages, 9 illustrations, bibliography and index. Cambridge, England, at the University Press, 1915.

Preface. There are few people who cannot relate some apparently striking instance of animal intelligence; the majority of such cases, however, will not stand critical examination. The science which has for its object the systematic investigation of the brute mind is Animal Psychology, and it would seem that the methods of this youthful discipline are still unknown to many, even among those who profess an interest in animal conduct. It is, then, with the purpose of presenting a brief account of the modes of procedure employed by Animal Psychology, its aims, trend, and the general nature of the results hitherto obtained, that this little book has been written. In a work of this character discussion and controversy would have been out of place, so the treatment has been confined as far as possible to description and illustration; at the same time attention has been drawn to some of the chief difficulties inherent in the inquiry. A complete and exhaustive presentation of facts was, of course, out of the question, and much that is of interest and importance has had, inevitably, to be omitted; but it is to be hoped that the interested reader of leisure will refer to some, at least, of the original articles mentioned in the bibliography, nearly all of which will be found to contain further references.

Under the headings Protozoan behavior; retentiveness: habit-formation, associative memory and sensory discrimination, instinct, homing, imitation, and the evidence for intelligence and for ideas, the author gives a most readable and informing account of the newer work on Animal Behavior. The book is written as a sketch and that plan of treatment is followed perfectly—with no lapses into detail and with a happy exclusion of technicalities.

The author's purpose is to present a review of the investigations in the field of animal behavior and to point out the main views which are now current. Concrete illustrations of experimental results are given, conclusions are weighed and matters calling for further study indicated. The needs of both the layman and the behaviorist are met by this essay. H. H. D.

THE CLINICAL ANATOMY OF THE GASTRO-INTESTINAL TRACT, T. Wingate Todd, M.B., Ch.B., F.R.C.S. (Eng.), Henry Willson Payne Professor of Anatomy in the Western Reserve University, Cleveland, Ohio; late Lecturer in Anatomy, University of Manchester, 264 pages, 32 illustrations, Index of authors quoted and a subject Index, Manchester at the University Press. Longmans, Green & Co., London and New York, 1915. \$1.75.

THE SOUND-TRANSMITTING APPARATUS IN NECTURUS

H. D. REED

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SIX FIGURES

The sound-transmitting apparatus of *Necturus* having been the subject of so much investigation, further comment would seem unnecessary. The results gained from the study of this apparatus in other groups of urodeles, however, and the uniform conclusions of Kingsbury ('05) and Norris ('11) and the significance of Herrick's ('14) and Brunner's ('14) observations bearing upon the rank of *Necturus* among tailed amphibia, demand a further investigation of the subject in order to determine the precise origin of every portion of the apparatus. Further study seems especially important when coupling the evident neotitic status of this species with conclusions which accordingly might be drawn regarding the nature of the fenestral elements.

In *Necturus* the sound-transmitting apparatus is composed of a single plate that accurately fills the somewhat elliptical foramen vestibuli of the mature animal and is connected by a well-defined stilus with the suspensorium of the jaws. Any relation with other extraotic elements is wanting entirely.

In typical urodeles, as for example the Amblystomidae, this apparatus is a double structure (Kingsbury and Reed '08). It is composed of a cephalic piece, the columella, and a caudal portion, the operculum. Each element is distinct in its origin and they are, therefore, without morphologic relations. Of the two elements the columella is the first to appear and develops wholly outside and independent of the ear capsule, only secondarily coming to lie against the membrane of the fenestra. It is essentially a flat plate connected with the suspensorium by a stilus. The columella becomes definitive in larval life and is to

be considered as the more primitive of the fenestral elements. Upon the assumption of a terrestrial existence, the columella apparently becomes functionless and fuses wholly or in part with the ear capsule, while a new element, the operculum, becomes *cut out* from the walls of the capsule just caudad of the primary fenestra. The operculum bears a perilymphatic prominence from which the *M. opercularis* extends to the shoulder girdle. It is important to note that these elements are not only different in origin, but each possesses distinctive skeletal relations; the columella with the suspensorium, the operculum with the shoulder girdle.

As mentioned above, the sound-transmitting apparatus of *Necturus* is composed of a single plate which possesses the anatomical relations of the columella of the amblystomid forms. In the *Plethodontidae* the sound-transmitting apparatus is in the form of a single plate filling the fenestra, but unlike that of *Necturus*, the plate in this family possesses the anatomical relations of both columella and operculum; that is, the cephalic end is connected with the suspensorium of the jaws by a stilus, while the caudal end comes into relation with the shoulder girdle through the *M. opercularis*. Development shows that the morphology of the plate is in harmony with these conditions. It is a double structure; the columellar portion arises outside the ear capsule, while the opercular portion is formed from otic cells which unite during development with the columellar element, producing a single definitive plate, the components of which differ in their morphologic nature.

Conclusions appear to be uniformly in favor of a greater structural similarity between *Necturus* and the larvae of the *plethodontids* than with those of any other group. In view of this and what has been said above respecting the characteristics of the fenestral elements in various urodeles, it seemed advisable to examine as complete a series of embryos and larvae as it was possible to obtain. The following were accordingly studied:¹ embryos 11, 12, 15, 16, 17, 18, 19 and 20 mm. long, and larvae

¹ An important gap in the series was filled by the generous loan of preparations of the 44 mm. stage by Prof. H. H. Wilder.

21, 22, 23, 24, 25, 26, 35, 40, 44, 48 and 70 mm. in length, respectively. The chief difficulty in arriving at conclusions respecting the morphology of the fenestral elements is the determination of the exact origin of parts. For the embryonic stages specimens 1, or at most 3 mm., apart in length proved satisfactory. Different specimens of a given length vary with regard to internal conditions of development. By employing several specimens of the various lengths it is possible to obtain every step in the development between two given stages and one is thereby enabled to trace the origin of elements cell by cell.

It is very evident that embryos from 15 to 20 mm. in length are the important stages in determining the origin of the columella in this species. A careful study of these series substantiates in every respect the conclusions of Platt ('97) and Kingsbury ('03) that in its origin the columella is independent of the ear capsule. It arises as a cord of cells extending between the squamosum and the fenestra vestibuli, but at all times in these early stages is clearly independent of both ear capsule and fenestral membrane. While all stages are necessary in tracing the development history of the fenestral structures, larvae from 35 to 70 mm. long are most important in determining the morphology of the plate itself.

The definitive plate in *Necturus* has a double origin, a suggestion made by Kingsbury and Reed ('09) as one of two possible interpretations of its nature.

Previous work renders it unnecessary to describe any given stage in detail. Only a brief sketch, therefore, will be given of the developmental changes taking place during the larval period. In larvae 23 mm. long the nature and relations of the columella are shown in figure 1. It consists in this stage of a well-defined chondrified rod extending from the level of the cephalic lips a third of the way across the fenestra. It is entirely free from all other skeletal structures, a relation which exists from its first appearance up to this stage. No stilus is present, the suspensorial connection being effected by the usual cord of cells. The structure and relations of the columella at this stage are very suggestive of similar stages in *Spelerpes* and as much in contrast

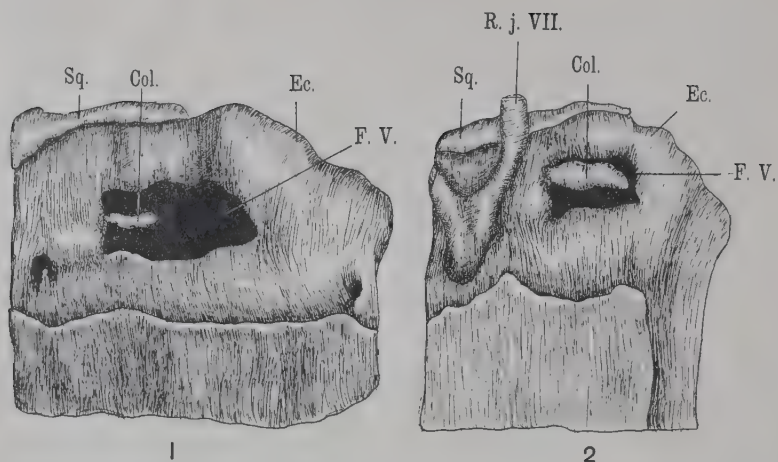


Fig. 1 Drawing from a wax model of the ear capsule of a larval *Necturus* 23 mm. long. *Col.*, columella resting against the fenestral membrane; it is rod-like, without stilus, and is free from the skeletal parts of the ear capsule; *Ec.*, ear capsule; *F.V.*, fenestra vestibuli; *Sq.*, squamosum.

Fig. 2 Drawing from a wax model of the ear capsule of a larval *Necturus* 25 mm. long. *Col.*, columella which has increased greatly in length and vertical diameter but is still without a stilus; *Ec.*, ear capsule; *F.V.*, foramen vestibuli; *R.j.VII*, ramus jugularis of the nervus facialis; *Sq.*, squamosal.

to the conditions which obtain in *Cryptobranchus* and *Amblystoma*, where the fenestral end of the columellar cord even before chondrification begins, spreads out over the membrane to form the plate portion of this element.

An examination of a specimen 25 mm. long (fig. 2) shows that the columella has increased greatly in size as regards both diameter and length. Its increase in size is relatively greater than that of the fenestra. It is still free from the ear capsule and without a stilus. The growth of the columella combines the features of *Amblystoma* (Kingsbury and Reed '08) and *Spelerpes* (Reed '14) a condition which is not found in other urodeles, so far as they have been studied, unless the growth of this structure in *Amphiuma* is to be so interpreted. Increase in the size of the stilus is at first apparently uniform, so that the cylindrical shape is maintained. But beginning with the 25 mm. stage, growth is most active along the dorsal side and particularly

in the cephalic end. This method of growth causes the former rod to become more plate-like and while it lies wholly outside the fenestral membrane it rests against it. The nature of the whole plate is best shown in a series of sections of a specimen 40 mm. long. A section near the cephalic end (fig. 3) shows the columella filling the fenestra at that level. The shape of the plate indicates its rapid dorsal and slight ventral growth, and further, this stage (and others younger) shows clearly from the position of the columella *upon* the fenestral membrane and the method of growth of its peripheral cells that no otic tissue has taken part in its formation. Such is not the condition further caudad. In following this series in that direction one notes that the thickened central part gradually narrows with a corresponding increase in the width of the thin portion both above and below (fig. 4). Finally, behind the middle of the fenestra, the thicker portion comes to a point and disappears entirely. Thus the thick portion forms a triangular area, with the apex pointing caudad and the base filling the cephalic part of the fenestra. In models as well as in sections the thick and thin regions are clearly marked (fig. 5). These two areas possess a deeper significance than that of mere topography. The thickened area represents columella resulting from the growth of the original extraotic rod, mentioned above and illustrated in figures 1 and 2. The thin portion of the plate arises as chondroblasts within the fenestral membrane independent of the columellar element. Figure 6 is from a section a little caudad of the middle of the plate. Here the thick columellar portion is in strong contrast with the thinner part of the plate found above and below. Both figures 4 and 6 show the mode of development of the thin part of the fenestral element. In the fenestral membrane near the edge of the previously formed plate, chondroblasts arise and through the subsequently secreted matrix come in contact with the edge of the plate itself. Thus new layers of tissue, the cells of which are derived from the fenestral membrane, are gradually added to the margin of the plate. This process, illustrated in figures 4 and 6, is quite different from that which obtains in the cephalic part of the plate, where it spreads out

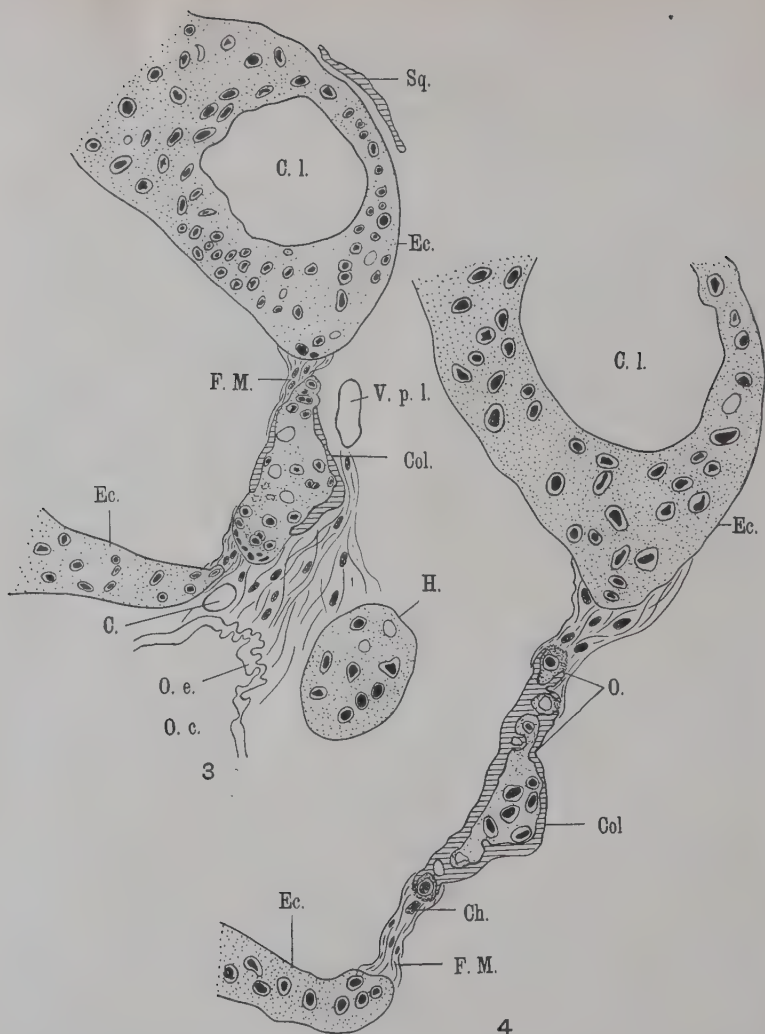


Fig. 3 Transsection of the ear capsule of a larval *Necturus* 40 mm. long, through the cephalic part of the fenestra. *C.*, arteria carotis interna; *C. l.*, canalis lateralis; *Col.*, columella spreading out over the fenestral membrane due to the proliferation of cells from its dorsal and ventral borders; *Ec.*, ear capsule; *F. M.*, fenestral membrane applied to the ental side of the columella only; *H.*, hyoid; *O. c.*, oral cavity; *O. e.*, oral epithelium; *Sq.*, squamosum; *V. p. l.*, vena petrosolateralis.

Fig. 4 Transsection of the ear capsule of a larval *Necturus* 40 mm. long, at a level of the middle of the fenestra. *Ch.*, chondroblasts forming in the fenestral membrane independent of columellar tissue; *Col.*, columella; *C. l.*, canalis lateralis; *Ec.*, ear capsule; *F. M.*, fenestral membrane; *O.*, otic portion of fenestral plate (operculum) formed by chondroblasts in the fenestral membrane, which are later surrounded by bony tissue and thereby joined to the definitive plate.

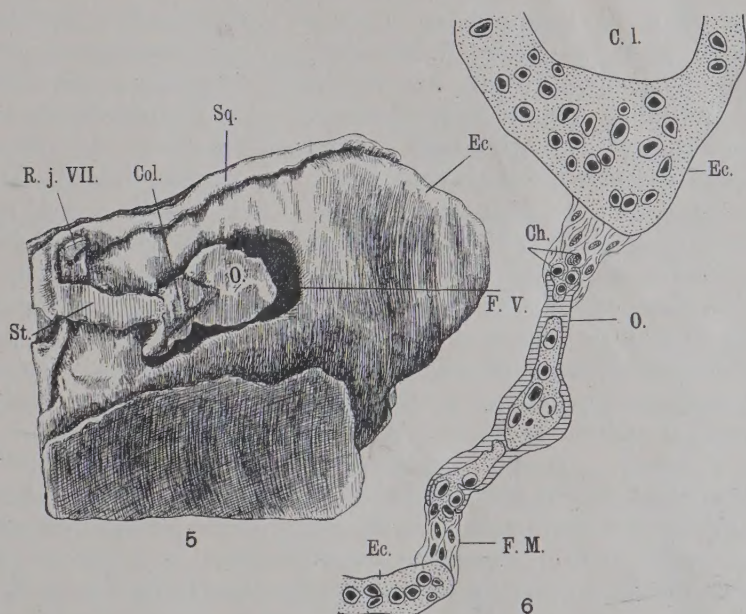


Fig. 5 Drawing from a wax model of the ear capsule of a larval *Necturus* 48 mm. long. *Col.*, columella portion of fenestral plate derived from tissue outside the ear capsule; *Ec.*, ear capsule; *F.V.*, foramen vestibuli; *O.*, otic portion of fenestral plate derived from chondroblasts in the fenestral membrane and comparable to the operculum of *Amblystoma* in origin and position; *R.j.VII.*, ramus jugularis of the *N. facialis*; *Sq.*, squamosal; *St.*, stylus columellae.

Fig. 6 Transsection of the ear capsule of a larval *Necturus* 40 mm. long, just caudad of the middle of the fenestra. *Ch.*, chondroblasts in the fenestral membrane; *C.L.*, canalis lateralis; *Ec.*, ear capsule; *F.M.*, fenestral membrane; *O.*, otic portion of the fenestral plate. At this level the columellar portion has almost disappeared; compare with figure 5.

over the fenestral membrane through the growth of its own tissue, as is shown in figure 3.

Transsections during this stage of development show that the fenestral plate of *Necturus* possesses numerous areas of cartilage encircled by bone, so that it exhibits a decidedly ringed appearance. This is due to the mode of ossification in connection with the formation of cartilage about the periphery of the plate. As in *Amblystoma*, two plates of bone are formed,

one upon the inner surface of the columellar portion and the other upon the outer. When growth of the cartilage ceases these plates meet above and below, thus forming a complete shell to this element. New chondroblasts in the membrane are consequently prevented from fusing with the previously formed cartilage and in the end become joined only through the extension of bony tissue about them in groups, or individually, as may be seen by a glance at the figures, where various stages in the extension of bone are shown. In many cases every stage in the formation and growth of cartilage and its inclusion by bony tissue may be seen in the same section. It is this method of independent origin of cells in the membrane and their fusion through ossification into a connected whole that accounts for the peculiar relations of the two elements shown in figures 4 and 6.

It appears evident from a study of the material available that the fenestral plate in *Necturus* is of double origin. The anterior end and a portion of the center being formed from the columella proton represents that structure in *Amblystoma*. The caudal half being formed by the chondrification of the fenestral membrane belongs to the ear capsule and must be likened, therefore, to the operculum of *Amblystoma*, although the *M. opercularis* never appears. The plate, as a whole, in its morphological nature is like that of *Spelerpes*, the difference being found in degree only.

Otic connections of the fenestral plate. There appears in the literature (Wilder '03) some comment concerning a connection between the fenestral plate in *Necturus* and the otic capsule. Since this element is free from the ear capsule in young larvae and since there is no continuity between the two structures in the adult it appeared advisable to examine the various series carefully with this point in mind, for in the light of such connections in other forms, an early fusion and a later separation of the parts did not seem probable. As stated above, the position of the columellar proton is along the fenestra, outside the membrane. Chondrification begins in larvae about 22 mm. long and at this stage the columella is clearly distinct from the ear capsule. Very soon, however, it comes to lie close to the

fenestral membrane, in which a decided impression is made. In somewhat older larvae (25 to 26 mm.) the cephalic and dorsal growth causes the columella to press closely against the lips of the fenestra, bringing about a relation which is maintained throughout life. In most instances the perichondrium, where the two structures meet, can be made out and in no place does there appear what might be considered a true fusion, but rather a firm articulation. An examination of the articulation in the adult strengthens the view that the lips of the ear capsule do not fuse with the fenestral plate and contribute nothing to its formation. The close relations may result from physical causes alone, since the plate of the adult exactly fills the fenestra, or may be considered as reminiscent of such fusions as occur in *Amblystoma* and others.

The stilus. It is a well established fact that the stilus in *Necturus* and *Proteus* is found below the jugularis branch of the facial nerve, a relation which is not the usual one among urodeles. It is believed, however, that this relation does not affect its homology with the stilus of other forms, a view which seems to be supported by the relations of columella and nerve which obtain in certain of the plethodontids. One observes that in the *Amblystomidae* the ramus jugularis VII comes forth freely underneath the stilus columellae and follows a course caudad across the ventral portion of the fenestra and its plate. In the *Plethodontidae*—as *Gyrinophilus*, for example—it emerges close against the ventral border of the stilus, and turning somewhat abruptly, takes a dorsal course across the fenestral plate. Whatever may have been the cause of the difference in the relative position of nerve and skeletal parts in these groups, it offers a possible explanation of the existing relations in *Necturus*. The nerve not only has a more dorsal position, but is well defined before the mesenchyme becomes concentrated into the forerunner of the columella. The latter naturally develops underneath instead of above it. The apparent mingling of the R. jugularis VII and the cells of the columellar proton in some plethodontid embryos tends to strengthen such a belief.

Summary. The fenestral plate in *Necturus*, while of the single type, is double in its origin. The columellar portion is extra-otic, having no early developmental connection with the ear capsule. At about the beginning of larval life it spreads out over the fenestral membrane and completely fills the cephalic portion of the fenestra, from which position it gradually narrows, coming to a point and disappearing near the center of the oval window. The remaining portion (by far the larger) of the fenestra is filled by tissue originating from chondroblasts in the fenestral membrane and therefore strictly otic. The columellar portion including the stilus is the homolog of the columella of *Amblystoma*. The otic part of the plate represents the operculum. The larval characteristics of the plate are shown *not* in its morphology but in the absence of the *M. opercularis*. The sound-transmitting apparatus of this species is a true morphologic intermediate between that of *Amblystoma* and the *Plethodontidae*.

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